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Original Communications

THE L. E. CELL TEST

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THE L. E. cell test is an empirical procedure which has proved to be of inestimable value in the diagnosis of systemic lupus erythematosus (SLE). The test is based on the presence of an unknown abnormal substance in the plasma and certain other body fluids of many patients with SLE. This abnormal substance under appropriate conditions is capable of inducing a peculiar and distinctive change in some leukocytes. The recognition of the specifically altered leukocyte, the "L. E. cell," is the end point of the test.

THE L. E. CELL PHENOMENON

L. E. cells were first discovered by Hargraves and his associates[1] in preparations of concentrated bone marrow from patients with SLE. It was thought at first that the peculiar cells had existed as such in the marrow *in vivo*. Studies soon demonstrated that L. E. cells are not seen in direct smears of marrow but are formed *in vitro* after the marrow has been withdrawn. Furthermore, L. E. cells are produced with equal rapidity in blood which is incubated *in vitro*, although they cannot be demonstrated in direct smears of peripheral blood. Certain facts concerning L. E. cell formation have now been abundantly confirmed.[2]

Editor's Note: This brief article is, we think, an extraordinarily concise, clear-cut, and up to the minute summary of the present situation as to the L. E. cell. Every sentence should be read. Because we believe that it should reach as wide an audience as possible of physicians interested in chronic illness, we take the unusual step of republishing it from the *Bulletin on Rheumatic Diseases*, Volume 7, Supplement No. 1, S-1, September, 1956, with the permission of the Editor of that *Bulletin* and of the author.

Alteration of leukocytes to form L. E. cells occurs in the presence of a factor contained in the plasma of many patients with SLE. This plasma factor can induce L. E. cell formation in leukocytes obtained from blood, marrow or other sources. In the presence of the plasma factor the L. E. cell transformation is readily produced with leukocytes obtained from normal individuals, from patients with many diseases and from a variety of animals.

The L. E. Cell.[1,2,3] A typical L. E. cell consists of a neutrophilic granulocyte distended by a large, homogeneous, globular inclusion body which compresses the segments of the nucleus against the cell membrane, leaving only a thin rim of cytoplasm. The inclusion body is characteristically larger than the nuclei of leukocytes, is structureless and hyaline in appearance, and is tinctorially distinguished from leukocyte nuclei by a somewhat more red and less blue coloring with Wright's stain. It is lysed by desoxyribonuclease, and the Feulgen reaction also indicates a nuclear origin. The inclusion body is derived from nuclear material released from other leukocytes and altered under the influence of the plasma L. E. factor to give it its distinctive appearance. The L. E. cell is formed when this altered nuclear material is ingested by a phagocytic cell. In positive L. E. cell preparations there are frequently extracellular masses of globular material, identical in appearance and staining reaction with the L. E. cell inclusion. Masses of the extracellular material are often surrounded by polymorphonuclear leukocytes, forming "rosettes." The relative numbers of L. E. cells, of extracellular masses and of rosettes vary with different patients and with the technique used in making the preparation.

The Plasma L. E. Factor.[2,3] The plasma L. E. factor is the substance in the plasma or serum of patients with SLE which is required for L. E. cell formation. At times this factor can be demonstrated in other body fluids. The factor has been shown to be an antigenically distinct component of the gamma globulin fraction of the serum proteins. Its activity is destroyed at 65° C. but persists after heating at 59° C., indicating that the factor is relatively heat stabile and that complement is not necessary for its action. Activity persists for at least several months when sterile serum or plasma is stored at low temperature. Plasma may be stored for many months in the frozen state without loss of activity. The source and nature of the plasma factor and its relationship to the lesions of SLE are unknown. SLE is a disease characterized by extraordinary serologic abnormalities, as evidenced by the frequent occurrence of abnormal distribution of the plasma proteins, biologic false-positive serologic tests for syphilis, positive cephalin and other flocculation tests, positive Coombs' tests and circulating anticoagulants. There is convincing evidence that the plasma L. E. factor is distinct from the proteins which give rise to the other serologic disturbances. There is no regular correlation between the occurrence of the L. E. factor and any of the other plasma abnormalities. The suggestion has been made that the L. E. factor may play an important role in the production of certain of the histologic lesions encountered in cases of lupus, in particular the hematoxylin bodies. The latter strongly resemble in structure the inclusion bodies of L. E. cells.[4] At present, however, there is no convincing evidence that clinical manifestations of SLE are dependent on the L. E. factor.

The mechanism by which the plasma factor brings about L. E. cell formation is not definitely understood. Most evidence at present suggests the view that the L. E. factor is responsible for a chemical alteration, probably depolymerization of desoxyribosenucleic acid in cell nuclei. This chemical change is thought to be responsible for the morphologic transformation of nuclear material to swollen, homogeneous globular masses which when ingested by leukocytes form the inclusion bodies of the L. E. cells. A theory that the L. E. factor has the character of an antibody against leukocytes has little to support it at this time.

It should be emphasized that the identification of L. E. cells is the only method currently available for detecting the presence of the L. E. plasma factor. The L. E. test is thus a unique bio-assay procedure.

Factors Influencing L. E. Cell Production.[2,5,6] L. E. cells are apparently rarely formed *in vivo* and are almost never seen in direct smears of the blood or marrow. However, after constrictive occlusion of the circulation of the finger, a few L. E. cells may be present in blood removed from a site distal to the occlusion. When blood is drawn from a vein, the rate of L. E. cell formation is influenced by a number of determinants. The degree of activity of the L. E. plasma factor is of prime importance, and without this factor no L. E. cells are produced. L. E. cell formation is completely inhibited by reduction of temperature to 4° C. However, there is little or no difference detected between rates of production at room temperature and at 37° C. Time is required for L. E. cells to be produced. In undisturbed heparinized blood, L. E. cells usually cannot be detected until about 10 minutes after the blood is drawn; thereafter their number rapidly increases during a period of at least 30 minutes. The type of anticoagulant seems to have little effect on the number of L. E. cells formed, but heparin is preferable because there is less distortion of the leukocytes. Oxalate in particular tends to distort cell nuclei, and sequestrene may alter the staining reaction of the L. E. cell inclusion bodies. If blood is allowed to clot L. E. production may be greatly enhanced. When heparinized blood is rotated in a tube or flask containing glass beads, there is a tremendous increase in the number of L. E. cells formed even though coagulation does not occur. The addition of a source of dead leukocytes to fresh blood has also been shown to facilitate L. E. cell production.

The absence of L. E. cells *in vivo* and their rapid appearance when blood is shed requires explanation. According to the theory of Hargraves,[2] the plasma L. E. factor is inert *in vivo* and must be "activated" in some way before L. E. cells are produced. Hargraves believes that blood coagulation and specifically the platelets play a role in this process. Other investigators have considered that other coagulation factors are essential. Another theory, suggested by recent observations,[5,6] is that L. E. cell formation may depend on the presence of non-viable leukocytes. The plasma factor, even though fully active *in vivo*, may be unable to attack living cells. The coagulation process may enhance L. E. cell formation solely as a result of injury to leukocytes, thus releasing nuclear material for transformation. Increased L. E. cell production brought about by rotation with glass beads seems best explained on the basis of trauma to leuko-

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cytes. In any event, some living and phagocytic leukocytes must be present to engulf the altered nuclear material and to complete the formation of L. E. cells.

TECHNIQUE OF THE L. E. CELL TEST

A number of methods have been described for demonstrating L. E. cells. In all of these the basic principles are the same. Plasma or serum from the patient who is thought to have SLE is brought in contact with leukocytes. After a period of time during which opportunity is provided for L. E. cells to be formed, the white cells are concentrated. Since L. E. cells may not be numerous, concentration of the leukocytes is essential if the method is to be reliable. A smear of concentrated leukocytes is stained with the usual blood stains and the preparation is examined systematically under the microscope for the distinctive cells. Methods employing heparinized, clotted or defibrinated blood have been extensively used, and are quite satisfactory when properly employed.[7] Under certain conditions, it is desirable to mix plasma from the patient in question with leukocytes obtained from other sources. This method is preferred when plasma must be stored or shipped before use, or when the patient has such severe granulocytopenia that satisfactory white cell concentrates cannot be obtained. Leukocytes may be obtained from compatible normal blood by removal of the buffy coat. Good results may be achieved by mixing the patient's plasma with blood or bone marrow obtained from dogs or other mammals.

The technique to be described in simple, effective and reliable. Relatively few manipulations are required in performing the test, and the patient's blood provides both the plasma and cellular elements required for L. E. cell formation. In positive preparations, L. E. cells and extracellular masses are usually very numerous, so that they can be recognized on brief examination of the preparation. Normal leukocytes are little distorted in this method, so that interpretation is not confused by the presence of numerous artifacts.

Method of Zinkham and Conley.[6] (1) Prepare 13 × 100 mm. test tubes by introducing into each tube 0.1 ml. of solution of sodium heparin, 10 mg. per ml. Allow the solution to dry so that the heparin adheres to the tube, which then contains 1 mg. of dry heparin. Cork the tube and store until used.

(2) Draw about 3 ml. of venous blood from the patient to be tested and introduce it into a tube containing heparin. Immediately cork the tube and invert several times to dissolve the heparin so that coagulation is prevented.

(3) Within 2 hours after the blood is drawn, place 5 glass beads, 5 mm. in diameter, in the tube containing the blood and place the tube in a Bryan-Garrey pipette rotor. Other similar rotating devices can be satisfactorily employed. Rotate the tube for 30 minutes at room temperature.

(4) Using a capillary pipette, transfer sufficient blood to fill a Wintrobe hematocrit tube. Centrifuge the hematocrit tube for 10 minutes at about 1000 r.p.m.

(5) Remove all but one or two millimeters of the supernatant plasma from the hematocrit tube with a capillary pipette and discard the plasma. Then, using the capillary pipette, carefully draw up the buffy coat and remaining plasma into the stem of the pipette.

(6) From the capillary pipette place a small drop of the buffy coat preparation on each of several coverslips. While holding one of the coverslips between the thumb and forefinger, place a clean coverslip on top, allow the fluid to spread, then pull the coverslips apart horizontally exactly as in preparing blood smears with coverslips.

(7) When the preparation has dried, stain the buffy coat preparation with Wright's stain. A longer period of staining is required than for blood smears. Allow the undiluted stain to remain on the smears for 1 minute, then add an equal quantity of distilled water. It is necessary to leave the diluted stain on the preparation for about 10 minutes for adequate staining. Rinse off the stain, and mount the coverslip in the usual way.

Interpretation. A satisfactory preparation is essential for adequate interpretation. With the rotation technique described, there is little apparent destruction of the blood cells, and most of the leukocytes should be intact and undistorted. Concentration of the white cells should be such that hundreds of cells are seen in each low power field, yet the cells should not be crowded together or overlapping. The cells should be well stained so that normal leukocytes are easily identified.

In positive preparations, three types of significant structures may be seen: L. E. cells, rosettes and extracellular globular masses having the appearance and staining reaction of the L. E. cell inclusions. At times the extracellular masses greatly predominate. In such instances, one expects to find L. E. cells on diligent search; however, the preparation is not reported as positive unless typical L. E. cells are seen. L. E. cells are larger than other leukocytes and because of their size and distinctive appearance are readily observed under the low power (100 ×) of the microscope. The area of two coverslips should be systematically scanned. In positive preparations, numerous L. E. cells are usually encountered. Structures resembling L. E. cells should be closely examined under the higher powers of the microscope. Certain structures which simulate L. E. cells may lead to a false-positive report unless rigid criteria are maintained for identification. Buffy coat preparations often contain leukocytes which have phagocytosed red cells, intact white cells, cell nuclei or other structures. In these phagocytes, the nucleus is displaced to the periphery of the cell as in an L. E. cell, but the inclusion is not identical with that of a typical L. E. cell. The characteristic L. E. cell inclusion is large, smooth, structureless and homogeneous, and is of a somewhat different color than the nuclei of leukocytes. Since an artifact may occasionally simulate an L. E. cell, a positive report should not be based on the finding of a single cell. In positive preparations, multiple L. E. cells as well as extracellular masses and rosettes are generally present. When only questionable cells are seen, or extracellular globular masses are encountered in the absence of L. E. cells, the test should be repeated, When a satisfactory preparation is entirely negative, however, it is unlikely that repeated tests at that time will yield positive results. Positive slides should always be saved because of the tremendous significance which is attached to a positive report. When a positive report is based on the finding of only a few L. E. cells, it is especially important that really typical cells be present and these should be marked

on the slide for reference. Ordinarily no attempt is made at precise quantification of the results of the test, although a crude estimate of the number of L. E. cells is of interest. Thus, L. E. cells may be reported as rare, occasional or numerous.

SIGNIFICANCE OF THE L. E. CELL TEST

SLE is a disease of unknown etiology with remarkably varied clinical manifestations. Pathognomonic clinical features are often lacking, and even at autopsy the diagnosis cannot always be established with certainty. There is no diagnostic test by which the disease can be invariably recognized. Thus, there is no standard of comparison for establishing the reliability of the L. E. cell test. Until means are discovered by which the diagnosis can be established with certainty, conclusions pertaining to the specificity of the L. E. cell can be only tentative.

Occurrence of Positive L. E. Cell Tests in Patients with SLE.[2,3] The blood of many patients with typical clinical manifestations of SLE can be demonstrated to form L. E. cells. There is no regular correlation between the severity of the disease and the number of L. E. cells produced. In some cases, L. E. cells become fewer or disappear with clinical improvement, whether the remission is spontaneous or induced by therapy. Some patients with unequivocal SLE cannot be demonstrated to form L. E. cells, even though the test is repeatedly performed using the best available techniques. L. E. cells at times cannot be demonstrated even in the terminal stages of the disease. In other cases L. E. cells may not be demonstrable early, but appear months or years after onset of the clinical manifestations. It is clear that a positive test is not an invariable accompaniment of the disease. Estimates of the incidence of positive tests in cases of lupus are meaningless, since the diagnosis is often not made when the test is negative, particularly in mild or early cases.

Specificity of the L. E. Cell Test.[2,3,7] In view of the many thousands of L. E. cell tests which have been performed, it is surprising that so few false-positive results have been reported. In fact, investigators with extensive experience doubt that true L. E. cells are formed unless the patient has SLE. There is no question that some of the reports of false-positive tests have been the result of improper interpretation of the preparations. Polymorphonuclear leukocytes which have engulfed lymphocyte nuclei have been mistaken for L. E. cells, as have other similar structures. L. E. preparations made from bone marrow may be misleading if the marrow contains amyloid, which may simulate an L. E. cell inclusion body. False-positive results have been reported in a few cases of rheumatoid arthritis, hemolytic anemia, and glomerulonephritis but in these cases it seems quite possible that the patient's disorder was a manifestation of SLE. Certainly many similar cases have been encountered in which other evidences of SLE appeared after a period of time. Of considerable interest is the occurrence of positive tests in association with certain drug reactions. A number of patients without previous evidence of SLE have developed a lupus-like syndrome after prolonged therapy with hydralazine and in some of these cases L. E. cells have been demonstrable.[8] Since the clinical manifestations

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simulate those of SLE, it would seem that the hydralazine had actually induced a syndrome closely related to lupus and under these circumstances the appearance of L. E. cells can hardly be considered a false-positive test. The reported rare occurrence of L. E. cells with other drug reactions, particularly penicillin hypersensitivity,[9] remains to be clarified. In the vast majority of penicillin and other drug reactions, L. E. cells cannot be demonstrated. It is noteworthy that a drug reaction may be the first manifestation of SLE. These considerations make it apparent that the finding of typical L. E. cells, confirmed by a repeated examination, has great diagnostic significance, and in most if not all cases indicates that the patient has SLE.

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THE NATURAL HISTORY OF SYSTEMIC LUPUS ERYTHEMATOSUS: AN APPROACH TO ITS STUDY THROUGH CHRONIC BIOLOGIC FALSE POSITIVE REACTORS

INTERIM REPORT

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IN MARCH, 1955, one of us (J.E.M.), with Lutz, reported a clinical study of 148 verified chronic biologic false positive (BFP) reactors in standard (lipid antigen) serologic tests for syphilis (STS). Each of these patients had been followed for one to twenty years after first discovery of the positive STS. There was a striking association between the chronic BFP phenomenon and the eventual development of verified systemic lupus erythematosus (SLE), or of an episodic form of chronic illness, the manifestations of which conform to those known to occur in SLE. The 1955 data are summarized in Table I.

TABLE I. ETIOLOGIC BACKGROUND IN 148 CHRONIC BFP REACTORS
(As of Nov. 1, 1954)

DIAGNOSIS		NO. OF CASES	PER CENT OF TOTAL	
SLE, verified		10	6.7	
Rheumatoid arthritis		7	4.7	41.8
SLE (or other collagen vascular disease) possible or probable		45	30.4	
Bizarre undiagnosed serious illness		5	3.4	
Clinically well	Dysgammaglobulinemia	43	29.0	
	BFP reactor only. No other abnormalities	13	8.7	
	Inadequately studied	25	16.9	
		148	99.8	

In briefest possible terms, 6.7 per cent had already developed verified SLE; 4.7 per cent had rheumatoid arthritis; and 30.4 per cent had experienced one

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or several clinical episodes highly suggestive of a widespread connective tissue disease, in some instances indistinguishable from the full-blown picture of SLE. Another 29 per cent, still clinically well, had laboratory evidence of dysgammaglobulinemia (DGG). Less than 9 per cent had no evidence, clinical or laboratory, of illness other than the chronic BFP phenomenon itself. Seventeen per cent were clinically well, but did not have adequate laboratory study other than the establishment of the BFP phenomenon.

On the basis of these observations, certain suggestions were made which are at variance with current opinion. These were:

1. That collagen vascular disease (CVD), and especially SLE, is not rare but instead is much more common than has heretofore been recognized.
2. That SLE is neither necessarily nor even often acute or subacute, but instead may be exceedingly chronic, lasting for many years or even decades.
3. That the clinical course of SLE is often relatively benign.
4. That SLE is not uniformly fatal.

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This altered concept of the character of SLE has been gradually evolved also by certain other workers, notable among them Harvey and his associates[2] from this Hospital, who have approached the problem from a different point of view.

At the risk of boring a sophisticated audience, we list briefly the major manifestations (excluding asymptomatic physical signs and laboratory abnormalities) of SLE. These number 26, and fall into 12 major categories (Table II).

They are presented afresh to emphasize several points: (a) that no patient with SLE has all of these manifestations; (b) that because of their nature, they usually occur in episodic fashion, punctuated by periods of remission; (c) *that no single one of these manifestations is in itself pathognomic of SLE*, and that each of them, taken separately, may be and often is associated with an illness of totally different cause (possibly excepting discoid LE and verrucous endocarditis); (d) that the appearance of any one of them alone does not justify even a tentative diagnosis of SLE; (e) that the occurrence of several of them, simultaneously or in succession over months or years, should arouse strong suspicion of this diagnosis; and (f) that the occurrence of enough of them, usually serially, can make the diagnosis practically certain even in the absence of laboratory confirmation. Just how many of these manifestations in combination, and which of them, serve to convince the individual observer will of course be the subject of heated debate.

The diagnosis of SLE is often overlooked, we believe, because of the very diversity of the clinical picture. The affected patient may, at one or another time, and because of one or another symptom, consult a general practitioner, internist, surgeon, dermatologist, orthopedist, ophthalmologist, neuropsychiatrist, or allergist. Each physician sees an episode; few have the opportunity of seeing the same patient in many different episodes. The vagueness, diffuseness, and chronicity of the disease all conspire to make early diagnosis difficult.

It is for this very reason that the group of chronic BFP reactors is so valuable for an understanding of the natural history, evolution, and course of at least some patients with SLE. For the most part, these patients are clinically well

TABLE II. THE MAJOR CLINICAL MANIFESTATION OF SLE

(Modified from Harvey and associates)

Systemic	Malaise, fatigability, weakness (as a major complaint) Fever; often prolonged, low grade, and episodic Weight loss Photosensitivity
Mucocutaneous	Discoid LE (butterfly rash) Urticaria—angioneurotic edema Various, often bizarre Subcutaneous nodules
Joints	Arthritis and/or arthralgia, often minor, hands and fingers Rheumatoid arthritis, sometimes deforming
Ocular	Cytoid bodies Uveitis, nongranulomatous, usually posterior
Serositis	Pleuritis Pericarditis
Pulmonary	Lupus pneumonitis
Vascular	Endocarditis, Libman-Sachs Myocarditis Vasospasm; Raynaud's phenomenon Phlebothrombosis, major, otherwise unexplained
Gastrointestinal	Various; usually vague; but including unexplained hemorrhage
Renal	Hematuria; nephritis
Hematologic	Anemia Purpura
Neuropsychiatric	Psychoses, various, often bizarre Convulsions
Allergic	Hypersensitivities, various; especially to drugs

at entry into the study, the starting point of which depends on the discovery, usually accidental, of a common laboratory abnormality. In them, prolonged periodic observation by a single group of observers permits the recording and dating of events as they occur, and on the basis of actual objective observations by the physician rather than on the retrospective memory of the patient.

The study of the chronic BFP reactors is continuing on a long-term basis, visualized as still to cover two or more decades. The 148 patients reported in March, 1955, have now increased to 210 in number. As of this report, we deliberately omit a statistical re-evaluation of the material. This has grown to a size and complexity which defies "hand analysis"; and coding and punch-carding are now in process (to be completed in perhaps two years).

Instead, we make this "Interim Report" on the basis of a few thumbnail sketches of six individual patients, not previously published, and chosen to illustrate our points.

(It must be recalled that verification of the chronic BFP phenomenon was not possible until the discovery of the treponemal immobilization test in late

1948; and that some of our patients, found to be seropositive with standard STS in earlier years, were originally managed as if they had latent syphilis.)

Case 1 (Fig. 1) is a 60-year-old woman who was first found to have a positive STS at the age of 36, nearly twenty-four years ago. Her status as a chronic BFP reactor was finally established in 1951. She has never had any clinical manifestation of SLE except various hypersensitivities; and is quite well and free from laboratory changes (other than the persistent BFP reaction) in 1956. This is the most benign type of clinical course, of which we have several examples.

J.H.H. 113433 (M.C.) W 40 F. Adm. 7-30-37

Age and Year	Event
Childhood - early adult	Intermittent hives; seasonal hay fever.
36 (1933)	Blood donor. STS +. Virgin. No R_x.
40 (1937)	Well. PE 0. STS + 10 units. CSF 0. Routine lab 0.
40-42 (1937-9)	Metal chemotherapy.
42 (1939)	Well. PE 0 except palpable liver and (?) spleen.
54 (1951)	Well. PE 0. STS + 8 units. TPI 0. DGG 0.
56 (1953)	Angioneurotic edema. PE 0. STS + 1 unit. TPI 0. DGG 0. LE cells 0.
60 (1956)	Well. No further evidence hypersensitivity. STS +. TPI 0. DGG 0. LE cells 0.

BFP reactor, duration 23 years. No other developments, clinical or laboratory, except hypersensitive state.

Fig. 1.

Case 2 (Fig. 2) is an example of severe rheumatoid arthritis. The suspicion of the BFP phenomenon was not aroused until late in her course, but was then verified. Even necropsy did not definitely establish the diagnosis, though the purpura, peripheral neuritis, and arterial lesions were consistent with the diagnosis of polyarteritis nodosa or of SLE. Certainly she falls into the category of connective-tissue disease, with a chronic episodic illness beginning fourteen years after the discovery of her first positive STS and lasting a further fifteen years until her death.

Case 3 (Fig. 3) is a clinically mysterious woman whose prolonged illness of twenty years' duration has many puzzling features. She has had at least 9 separate manifestations compatible with the diagnosis of SLE (Table II). The suspicion of this disease was first aroused in 1949, when the chronic BFP state was recognized; and the diagnosis was verified in 1952 by the demonstration (on several occasions and in three different laboratories) of LE cells. She is still alive and enjoying moderately poor health as of September, 1956, at least twenty years after the onset of clinical trouble; but LE cells have not been definitely redemonstrated since 1952 in spite of repeated search.

Case 4 (Fig. 4) is a remarkable example which introduces an uncommon manifestation of SLE, deep thrombophlebitis. She was first suspected of SLE in 1949, after the development of severe psychosis. Several efforts to persuade

J.H.H. 252956 (R.R.) W. 40 F. Adm. 1942

Age and Year	Event
Childhood - early adult	Good health:
24 (1926)	Lassitude. Routine STS+. Husband's STS 0. Metal chemotherapy elsewhere 11 yrs. No further anti-$\mathcal{L}$ R_x.
38 (1940)	Hysterectomy (menorrhagia). Coincidental polyarthritis, rheumatoid, large and small joints, severe, progressive, and deforming.
40 (1942)	PE for $\mathcal{L}$ 0. Severe arthritis, marked GGE, anemia. STS+ 2 u. CSF 0. CSR 23. No DGG. R_x gold. Some improvement. Gold dermatitis.
41-47 (1943-1949)	Arthritis inactive; severe residual deformities.
49 (1951)	Arthritis worse; steroid hormones; some improvement. STS+ 4 u. LE cells 0. BFP suspected, not proved.
51 (1953)	Joints smoldering. Ecchymoses and petechiae, unexplained. STS +. TPI 0. No DGG.
53 (1955)	Arthritis active; peripheral neuritis, hepatosplenomegaly. DGG++++ Steroid R_x; death from masked perforation gastric ulcer. Autopsy: – no definite SLE; peculiar healed and healing arterial lesions consistent with CVD (Rich),

Rheumatoid arthritis (? SLE) 15 yrs. duration in proved BFP reactor.

Fig. 2.

J.H.H. 415738 (H.T.) W. 34 F. Adm. 1947

Age and Year	Event
Childhood	Urticaria, angioneurotic edema, recurring episodically throughout life.
23-37 (1936-1950)	Intermittent migratory arthritis large joints (? palindromic, ? angioneuratic), lasting 15 yrs.
30 (1943)	STS now and later + 1 u. Metal chemotherapy.
34 (1947)	Pregnant. PE 0. STS +. CSR 32. R penicillin. Full term child, d. congenital deformities.
35 (1948)	Miscarriage 3 mos.
36 (1949)	Arthritis and urticaria persist. STS+. TPI 0.
37 (1950)	Headache (? migraine). Arthritis disappears; no further recurrence. Allergic rhinitis. Bizarre undiagnosed skin rash, erythematous edematous plaques, past 18 mos. STS +. TPI 0.
38 (1951)	Butterfly rash face. STS +. DGG and LE cells 0.
39 (1952)	Bizarre sciatic pain. Vaginal bleeding. Severe hypochondriasis. R_x cortisone, no effect. Operations: I.V. disc, hysterectomy; no improvement. TPI 0. LE cells + in several preps (3 labs).
40 (1953)	Bizarre severe abdominal pain; (?) hematuria. Anxiety depression. Exploratory laparotomy 0. LE cells 0.
39-43 (1952-1956)	Past 5 yrs. 12 hospital adm. (1 hosp. only; pt. also in others); 119 hosp. days; 267 pp. hosp. history, 4 operations; hypochondriasis continues. Psychiatrist refused. LE preps repeatedly "suspicious", not def. +.
43 (1956)	Fairly well. Enjoys poor health. No definite manifestations except bizarre skin rashes, allergies.

SLE proved; duration ? but probably 30 + yrs. Bizarre manifestations. BFP reactor 16 yrs.

Fig. 3.

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the psychiatrists to investigate the possible diagnosis by appropriate laboratory tests were unsuccessful, and did not prevent drastic and perhaps unnecessary psychiatric treatment. Fourteen years after onset, and 6 episodes of illness later, the diagnosis of SLE is finally verified. She is quite well and in full remission, as of September, 1956.

J. Head *W 21 F* *Adm 7-2-48*

Age – Year	Event
Childhood on	Migraine
14 (1941)	Femoral thrombophlebitis, left. Cause?
20 (1947)	"Maladjusted". Psychoanalysis.
21 (May 1948)	Femoral thrombophlebitis, right. Cause? STS +. CSF 0. Anemic.
21 (July 1948)	P.E. 0. STS + 2 units. CSR 33. Ht 37 Hgb. 12.2
22 (Oct. 1948)	Ulcerative indurated lesion left ankle, lasting 2 mos. Diagnosis? Severe conjunctivitis.
22 (May 1949)	Depressed. Psychiatric diagnosis schizophrenia. STS + 1 unit. TPI 0. Not now Anemic. P.E. 0.
23 (1950)	Electric shock; insulin coma.
24 (1951)	No psychiatric improvement. Topectomy!! Brain biopsy 0.
26 (1953)	Discharged from psychiatric hospital.
29-30 (Sept. 1955)	Discoid L.E. face (1 mo.) Hemorrhagic papular lesions legs. Thrombocytopenia. L.E. cells +. Metacorten remission.
31 (Oct. 1, 1956)	Grumbling arthralgia, fibrositis fall 1955 - summer 1956. Now full remission without steroids past 2 mos. Psyche OK except "emotional instability." Working.

S.L.E. verified after probable 16 year course.

Fig. 4.

The next case (Case 5, Fig. 5) might be the medical twin sister of the patient described in Fig. 4. She was found to be seropositive as a young woman of 20. Since then, she has had 12 episodes of illness compatible with the diagnosis of SLE (over an eighteen-year period), including (as in Case 4) deep thrombophlebitis and a serious psychosis. With her, we found it impossible to persuade a reluctant psychiatrist in another city that the possibility of SLE should be entertained. He thought the patient should not be disturbed with such nonsense. Since then (1954) she has had two further episodes of physical illness, each of increasing severity.

The next patient (Case 6, Fig. 6) represents SLE almost at its worst. Her course began in 1942 with the BFP phenomenon, at first interpreted, of course, as syphilis. In the ensuing fourteen years, she has had multiple episodes of SLE (the diagnosis first suspected in this clinic in 1948 and verified in 1950). On at least 5 occasions, from 1951 to 1956, she has been thought to be moribund because of pericardial tamponade, status epilepticus, renal failure, and recurring severe infections. Nonetheless, she survived these and her disease was seemingly under control on prednisone, 25 mg. daily, until October, 1956, when she committed suicide.

E.M.Cou W 26 F Adm. 10-29-42

Age - Year	Event
20 (1938)	Routine STS +. Pt. well.
25 (1941)	Pleuritis with fluid. Hematuria 10 days.
26 (1942)	P.E. O. CSR 38.
27 (1943)	Bilateral deep femoral thrombophebitis.
30-33 (1946-1949)	Repeated medical checks (elsewhere) for malaise. Hepatomegaly. anemia; CSR 43.
33 (Nov. 1949)	P.E. O. STS + 16 u. TPI O.
33-36 (1949-1952)	Migraine.
21-36 (1941-1952)	Fleeting arthralgia in fingers.
34-36 (1950-1952)	Hay fever; hives.
36 (Nov. 1952)	P.E. O. except mild pretibial edema. No anemia. DGG. LE cells O. STS +. TPI O.
37 (Dec. 1953)	Toxemia; miscarriage; subsequent acute psychosis. Diag. (elsewhere) schizophrenia. No lab data.
38 (Dec. 1954)	Psychiatric recovery. Miscarriage 5 mos. STS +.
39 (April 1955)	Rosacea nose and chin for 1 yr. Mild hypertension 162/85. Diastolic murmur (? Libman-Sachs). Glob. 3.1.
40 (Dec. 1955)	Sudden dysarthria; left arm weak, ataxic. CSF O except protein 51 mg./%.
40 (May 1956)	Residual mild left hemiparesis. STS +. Air injection:- cortical atrophy: Cause ?

Probable SLE - 18 years' course.

Fig. 5.

J.H.H. 546814 (C.T.B.) *W 27 F* *Adm 7-14-48*

Age — Year	Event
21 (July 1942)	STS + No Rx.
21 (Aug-Dec. 1942)	Polyarthritis, fever 4 mos. Diag. rheumatic fever.
22 (Spring 1943)	Polyarthritis, recurrent, 1-2 weeks.
23 (1944)	STS + No Rx.
24 (1945)	Polyarthitis, recurrent, 2-3 wks. Antisyphilitic Rx given.
27 (July 1948)	Referred as seroresisant syphilitic. Depressed, Anemic P.E. O. STS+8u.
27-29 (1948-1950)	Intermittent brief recurring arthritis. 13 lbs. weight loss. Sore finger tips. Depression.
29 (July 1950)	P.E. O, except arthritis right great toe. STS + 8u. TPI O Anemia L.E. cells +.
30 (Nov. 1951)	Pericarditis; status epilepticus; renal failure; psychosis. In extremis 3—4 wks. L.E. cells +.
31 (June 1952)	See photograph of patient.
32 (Nov. 1953)	Urinary infection. E coli bacteremia.
33 (April 1954)	Nephrotic syndrome, hypertension, anemia, multiple transfusions.
33 (Dec. 1954)	Condition desperate. Renal Biopsy; local hydrocortisone; L.E. +.
34 (1955)	Acute pelvic abcess drained.
35 (Feb. 1956)	Pyarthrosis right knee, with rupture into calf muscles. Drainage; partial excision gastrocnemius; walking cast.
35 (Oct. 1 1956)	Fairly well. S.L.E. controlled by 25 mg. prednisone. Nephrotic edema controlled neohydrin.

S.L.E. 14 yrs. duration. Still living after repeated lupus and infectious crises. (Oct. 1956 death by suicide.)

Fig. 6.

Our six cases, here presented, have illustrated: (1) the chronicity of the disease entity under discussion, the patients having been under personal observation for 23, 29, 20, 16, 18, and 14 years, respectively; (2) its episodic nature; (3) the difficulty of early diagnosis; (4) the great variety of its clinical manifestations; and (5) the variability of its course, from completely uneventful to fatal.

* * * * * *

Medical knowledge of SLE in 1956 may be aptly compared with the state of affairs as to syphilis in the years 1493 to 1903. Like SLE, syphilis too is a chronic disease of many years' duration; its etiology was in doubt until 1903, as is that of SLE now. Like SLE, syphilis too could and does affect many tissues and structures of the body, with episodes of illness involving the mucocutaneous, cardiovascular, and nervous systems, and many if not all of the visceral structures. Weeks, months, or many years might separate individual episodes. For 4 centuries, there was medical debate as to whether a particular manifestation or syndrome was or was not due to syphilis; and elaborate statistical studies were carried out to prove or disprove individual points. All of this was abruptly ended in the five-year period, 1903 to 1907, with the discoveries of the *T. pallidum* and the serologic tests of Wassermann, Neisser, and Bruck. The pieces of the jig-saw puzzle fell neatly into place; and at once it became clear that a chancre and a saccular aneurysm were in fact due to the same cause and were episodes of the same chronic illness, although separated by many years in time.

There is as yet no such simple and convenient laboratory test for SLE. The LE cell phenomenon does not serve. As Conley clearly puts it[3]: "Some patients with unequivocal SLE cannot be demonstrated to form LE cells . . . (which also) may not be demonstrable early, but appear months or years after onset of the clinical manifestations. . . . Estimates of the incidence of positive tests . . . are meaningless, since the diagnosis is often not made when the test is negative, particularly in mild or early cases."

It seems possible that a workable diagnostic test for SLE may develop from further study of the disorders of globulin which develop in this (and other) diseases. Indeed, even now, in patients with suspicious clinical manifestations, the existing crude tests for DGG may serve as a rough screening device, with positive results strengthening clinical suspicion.

In summary, the problems presented by SLE and related connective tissue diseases are a fascinating clinical and experimental frontier demanding long-term study. Our own approach, through the avenue of the chronic BFP phenomenon, has contributed some important fragments of information, and offers great promise for further investigation.

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PULMONIC MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Report of Five Cases

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INTRODUCTION

PULMONIC manifestations may appear during any phase of systemic lupus erythematosis (SLE). They may be the first sign of the disease,[1] they may appear in the midst of an apparently tranquil remission, they may be the predominant clinical features throughout the entire course, or they may be the final overwhelming complication of the terminal stages. Respiratory involvement may be a clue to the diagnosis of SLE, particularly where there is recurrent or chronic pneumonitis or pleural effusion in a patient who has rheumatoid arthritis. The bizarre nature of the pulmonary changes causes them to simulate the specific lesions of many other diseases. This report presents a brief review of the recorded association of pneumonitis and systemic lupus erythematosus, and five case histories which illustrate unusual diagnostic and therapeutic pulmonary problems encountered in 154 patients with systemic lupus erythematosus who were seen at the Cleveland Clinic from 1949 through 1955.

HISTORICAL REVIEW

In 1903, Osler[2] described a pneumonitis that occurred in patients with systemic lupus erythematosus, and stressed that the course of the respiratory involvement was chronic and protracted. Rakov and Taylor[3] in 1942 were the first to report persistent lobar pneumonia in a patient who had systemic lupus erythematosus without skin lesions. More recently, Sante and Wyatt[4] stressed the concept that pulmonary manifestations may be a warning of the terminal stage of the disease. Israel[5] also reported the SLE-pulmonary disease association, and pointed out that pulmonary changes can occur during any phase of the

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malady. The fact that pathologic changes in the lungs in the course of systemic lupus erythematosus generally are unobtrusive has been well documented by the studies of Tumulty,[6] Purnell, Baggenstoss, and Olsen,[7] and Gould and Daves.[8]

The following five case reports illustrate the predominant respiratory manifestations that occurred in 154 of our patients during the course of systemic lupus erythematosus.

CASE REPORTS

CASE 1.—J. C., a 38-year-old white woman, was first admitted to Cleveland Clinic Hospital on July 13, 1950, with complaints of incapacitating weakness and shortness of breath of three months' duration. Six years previously, arthralgia of the knee joints associated with generalized weakness and loss in weight of 50 pounds, gradually had developed. Two years before admission, she had "severe pneumonia," followed by a two-week illness consisting of coughing, weakness, and repeated episodes of hemoptysis. The dyspnea and weakness became progressively more severe. An x-ray of the chest taken elsewhere in 1949 was reported to the patient as "negative."

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Fig. 1.—Case 1. Roentgenogram of chest.

Physical Examination.—Temperature was 99.5° F., pulse rate 132 beats per minute, and blood pressure 115/84 mm. Hg. Examination of the eyes, ears, nose, and throat gave negative results. There was slight diffuse enlargement of the thyroid gland. The heart was normal in size; there was normal sinus rhythm and no ectopic beats or murmurs could be heard. Examination of the lungs disclosed harsh breath sounds with a few scattered crepitant râles at the bases. The liver, spleen, and kidneys were not palpable. Rectal examination gave essentially negative

results. The extremities showed moderate limitation of motion in all directions because of periarticular soft-tissue swelling and plus 1 pitting edema of the ankles.

An x-ray of the chest revealed slight pulmonary congestion bilaterally, and a patchy area of pneumonitis in the right mid-lung field (Fig. 1).

Laboratory Tests.—Leukocyte count was 7,450 and erythrocyte count 4,700,000 per cubic millimeter. The urine had a specific gravity of 1.018, a trace of albumin, rare erythrocytes and 10 to 20 leukocytes per high-power field, and tests were negative for sugar and acetone. Blood sugar content was 27 mg., carbon dioxide-combining power 53.2 ml., and serum chloride level 495 mg. per 100 ml. Gastric analysis revealed a gastric content of 45 ml. with 19 units of free hydrochloric acid and a total of 49 units of acid.

Course.—The initial clinical diagnosis of this patient's condition was hyperthyroidism, and she was treated with propylthiouracil, 100 mg. three times daily, and Lugol's solution, 10 drops three times daily. On July 21, eight days after admission, in the absence of appreciable improvement this therapy was discontinued. Systemic lupus erythematosus was suspected because of the past history of recurrent arthralgia and pneumonia coupled with the predominant pulmonary complaints on this admission. This diagnosis was confirmed by a strongly positive LE test. Cortisone and penicillin therapy was started, but no beneficial change in the patient's condition ensued. On July 22, the serum chloride level was 462 mg. per 100 ml., sodium 133 meq. and potassium 5.1 meq. per liter, and the leukocyte count was 23,950 per cubic millimeter, with 92 per cent polymorphonuclear leukocytes and 8 per cent lymphocytes. On July 23, ten days after admission, the patient died. At autopsy the pulmonary tissue demonstrated severe, partly confluent bronchopneumonia, perivascular fibrosis in the pulmonary vessels, and chronic pleuritis.

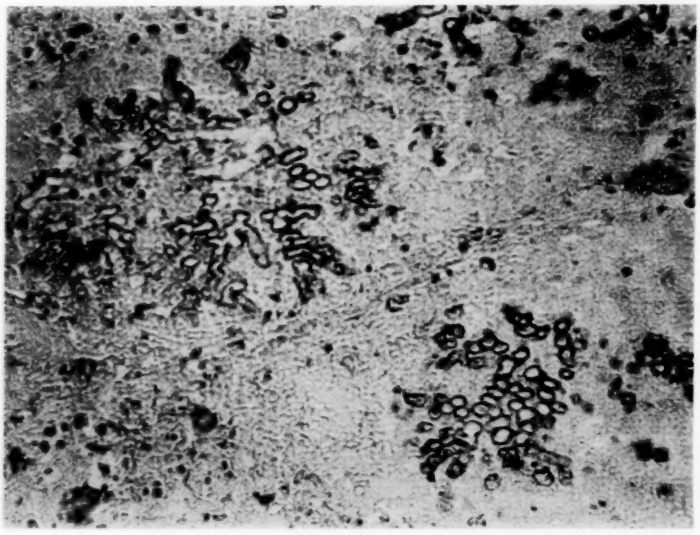

Fig. 2.—Case 2. Photomicrograph of right lung, showing fungi and changes described in text, with entensive necrosis of bronchi and bronchioles of infarct type with masses of polymorphonuclear leukocytes and clumps of bacteria with rather numerous masses of fungi, etc. (×460.)

Case 2.—C. H., a 17-year-old white woman, was first admitted to Cleveland Clinic Hospital on June 15, 1949, with a presenting complaint of profound weakness. Two years prior to admission, she had "pleurisy"—pain in the chest and fever. A year later, swelling and stiffness developed in the hands, elbows, feet, ankles, and knees. Three weeks before admission, she had

exertional dyspnea, minimal dyspnea at rest, and a temperature of 105° F. A thoracentesis was performed elsewhere, and removal of about 1 liter pleural fluid brought some relief. A week later, the patient developed a cough.

Physical Examination.—On admission the patient was feverish, debilitated, and in acute distress with profound weakness. Temperature was 101° F., pulse rate 94 beats per minute, blood pressure 108/60 mm. Hg, and respirations 18 to 20 per minute. There was a distinct erythematous scaly eruption over the nose, zygomata, and forehead. The soft and hard palates revealed several discrete ulcerations. There was bilateral swelling of the parotid and submandibular glands. The thyroid gland and lymph nodes were not palpable. Flatness and decreased respiratory sounds were present over the left pulmonic base posteriorly, and scattered moist râles were present diffusely throughout both pulmonic fields, particularly in the right lung. The heart was normal in size, and no murmurs or ectopic sounds were heard. The liver, spleen, and kidneys were not palpable. There was 1 plus swelling and some stiffness of the knee joints, and plus 1 swelling of the dorsa of both hands and both wrists. The elbow joints were slightly swollen.

An x-ray of the chest showed pneumonitis with scattered areas of infiltration in the right lung.

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Laboratory Tests.—Leukocyte count was 5,400 per cubic millimeter with a normal differential count. Urine showed plus 1 albumin, numerous erythrocytes per high-power field, specific gravity of 1.016, and negative tests for sugar and acetone. Sedimentation rate was 0.82 mm. per hour (Rourke-Ernstene). An LE test of the blood plasma was positive.

Course.—Treatment of this patient, who was in acute distress at the time of admission, consisted of penicillin and general supportive measures. (Steroids were not yet available.) On June 19, four days after admission, the temperature rose to 103° F. and she gradually lapsed into a coma. The next day the blood urea was 222 mg. per 100 ml. and shortly thereafter she died. At autopsy, tissue from the right lung revealed severe pneumonitis, bronchopneumonia, and bronchiolitis, and extensive necrosis of the bronchi and bronchioles with masses of polymorphonuclear leukocytes and clusters of bacteria and rather numerous masses of fungi growing as septate hyphae suggestive of the genus *Aspergillus* (Fig. 2).

CASE 3.—M. K., a 33-year-old white woman, was first admitted to Cleveland Clinic Hospital on Aug. 30, 1952, with a presenting complaint of persistent fever. Eight months previously, she had stiffness and pain of the proximal interphalangeal joints; and later, fever, sweats, chills, and weakness. Cortisone and ACTH therapy induced a remission of these symptoms. However, one month prior to admission, while still continuing steroid therapy, she had a flare-up of fever with a temperature of 105° F. During this exacerbation she was hospitalized elsewhere. Penicillin was administered but was of no benefit. The cortisone dosage was increased and the patient's condition improved. At the time of discharge from the first hospital she was taking 50 mg. of cortisone every 6 hours.

Physical Examination.—There was a butterfly papulomacular eruption over the face, particularly the nose and cheeks. Heart rate was 96 beats per minute, and blood pressure was 160/82 mm. Hg. Cardiac examination revealed a grade II systolic murmur in the pulmonic area. There were scattered coarse râles throughout both lung fields. Abdominal, pelvic, and rectal examinations gave normal results.

An x-ray of the chest revealed clear pulmonary fields and a generalized cardiac enlargement.

Laboratory Tests.—Blood hemoglobin content was 5.8 Gm. per 100 ml., and leukocyte count was 2,600 per cubic millimeter with a differential count of 93 per cent neutrophils and 7 per cent lymphocytes. An LE test was strongly positive.

Course.—The patient had an initially favorable response to cortisone and ACTH. However, as the renal status deteriorated, the level of urea nitrogen progressively became higher and the glomerular filtration rate became depressed. On September 11, twelve days after admission, an x-ray of the chest still revealed clear pulmonary fields. On September 12, blood urea content was 42 mg. per 100 ml., carbon dioxide-combining power 69 ml. per 100 ml., serum chloride level 84 meq., sodium 135 meq., and potassium 3.2 meq. per liter. Urea clearance was 14 per cent during the first hour and 12 per cent during the second hour. The sedimentation rate ranged from 0.8 to 0.5 mm. per hour (Rourke-Ernstene).

During the period from September 18 through 20, the patient had a dry, nonproductive cough, but examination of the lungs gave negative results. Treatment with penicillin and streptomycin was started. Because of transient psychotic reactions, the administration of cortisone and hydrocortisone was stopped temporarily on September 21; the patient was given ACTH intravenously for four days, and then ACTH intramuscularly 40 to 80 mg. daily in two to four divided doses. Terramycin also was administered orally, 250 mg. four times daily. On September 26, twenty-seven days after admission, x-ray of the chest revealed an infiltration in both lower pulmonary fields. On September 30, an LE test was negative. On October 3, thirty-four days after admission, blood hemoglobin was 5.4 Gm. per 100 ml. and leukocyte count was 2,400 per cubic millimeter, with 92 per cent neutrophils, 7 per cent lymphocytes, and 1 per cent monocytes. On the following day, generalized grand mal convulsions occurred. On October 6, thirty-seven days after admission, a severely protracted generalized seizure supervened, shortly after which the patient lapsed into coma and died.

At autopsy, microscopic sections of the lung revealed advanced hemorrhagic necrosis with complete disappearance of many alveolar structures; they had been replaced by masses of cell clusters and polyplike structures. Some alveoli appeared to be preserved. In one area, fungi were seen that resembled the genus *Aspergillus* (Fig. 3).

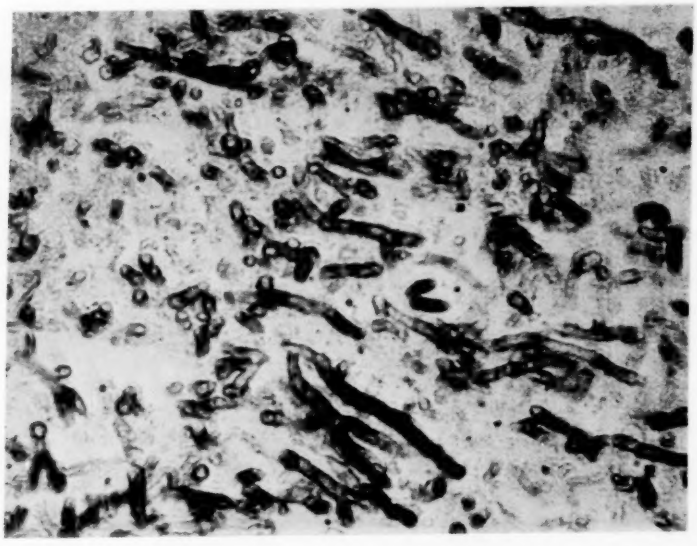


Fig. 3.—Case 3. Photomicrograph of section of lung showing organisms resembling *Aspergillus*. (×460.)

Case 3 is similar to Case 2 in respect to pathologic pulmonary findings on necropsy, but this patient (Case 3) had received extensive steroid therapy. In both cases, the fungi were morphologically similar to the genus *Aspergillus*.

CASE 4.—C. D., a 35-year-old white woman, was first admitted to Cleveland Clinic Hospital on Sept. 23, 1950, with a presenting complaint of pain in the joints of the fingers, elbows, ankles, and knees, of twelve months' duration. One month before admission she had an episode of fever and chills that lasted one week, moderate patchy loss of hair, and scaling and itching of the scalp. On admission, the hemoglobin was 12 Gm. per 100 ml., leukocyte count 4,100 per cubic millimeter, and sedimentation rate 0.78 mm. per hour (Rourke-Ernstene). An LE test was negative, but a clinical diagnosis of systemic lupus erythematosus was made. For six days the patient was given penicillin and supportive therapy. Since there was no substantial improvement in her condition, cortisone treatment was administered and dramatic improvement ensued. After

discharge from the hospital, the patient developed pneumonia and was treated by her family physician. After subsidence of the pneumonia, she discontinued the steroid treatment.

About one year later, on Oct. 15, 1951, the patient was seen for follow-up examination at the Cleveland Clinic and was hospitalized because of weakness, nausea, abdominal pain, and malaise. Five weeks previously, she developed chills, fever, pain in the chest, minimally productive cough, and her condition was roentgenographically diagnosed elsewhere as the result of pneumonia.

Physical Examination.—Examination revealed a well-developed, malnourished woman who appeared to be chronically ill. There was a diffuse erythematous maculopapular eruption on the face mainly below both eyes and around the nose and cheeks. Small cervical lymph nodes were palpable. The lungs were clear to auscultation and percussion. The heart was of normal size, and the rate was 152 beats per minute and regular. Blood pressure was 95/70 mm. Hg. The liver and spleen were not palpable. There was some phlebitis of the left thigh along the upper inner aspect, without associated trophic changes. There was slight swelling of the metacarpal joints of both hands and moderate swelling of the interphalangeal joints.

Laboratory Tests.—Serum sodium level was 128.5 meq. per liter, potassium 4.0 meq. per liter, blood sugar 97 mg. per 100 ml., sedimentation rate 1.7 mm. per hour (Rourke-Ernstene), urea nitrogen 24 mg. per 100 ml., carbon dioxide-combining power 41.9 per 100 ml., and serum chloride 95.9 meq. per liter. An LE test was positive.

Course.—Therapy included elevation of the left leg, application of warm packs, and oral administration of gelatin ACTH, 20 mg. daily. The phlebitis subsided gradually and the leg was normal within one week. Within 12 hours after the initial dose of ACTH had been given, there was a dramatic fall in the temperature to normal. On the sixth day in the hospital, the dosage of gelatin ACTH was increased to 20 mg. every four hours. The patient steadily improved, and on October 23, eight days after admission, she was discharged on a maintenance dosage of corticotropin, 10 units daily. She has continued to take that medication, and when last examined on June 23, 1955, four years and nine months after initial admission, there were no abnormal findings.

CASE 5.—C. F., a 29-year-old white woman, was first admitted to Cleveland Clinic Hospital on Jan. 19, 1950, with chief presenting complaints of easy fatigability and a skin eruption of about three months' duration. The eruption had appeared first over the bridge of the nose and gradually had spread over the entire face. Six weeks prior to admission she had a fever, and two weeks later she developed a cough and slight hemoptysis. Two weeks prior to admission, she was hospitalized elsewhere and a diagnosis of systemic lupus erythematosus was made.

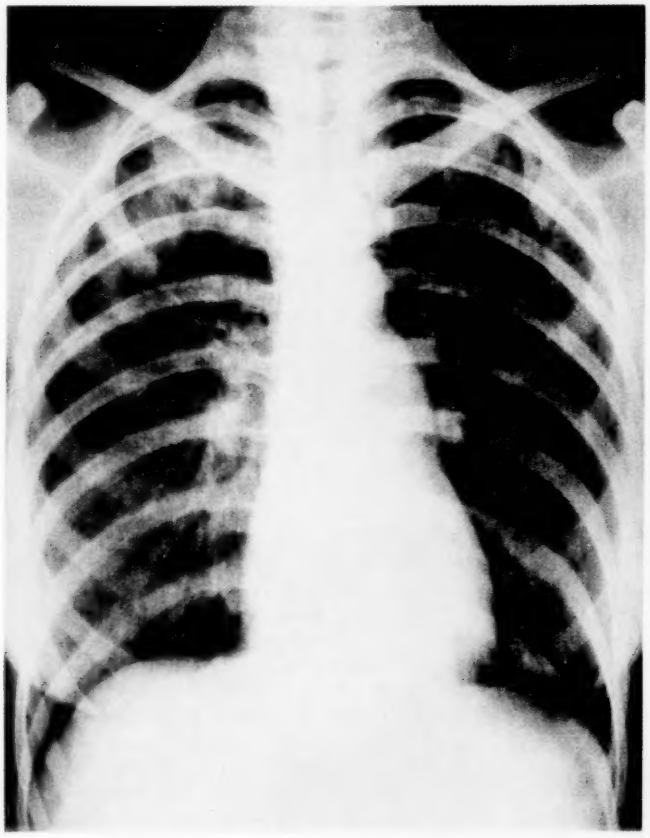
Physical Examination.—The patient had a diffuse maculopapular eruption extending from the bridge of the nose outward to the sides of the face. Temperature was 98.6° F., pulse 100 beats per minute, and blood pressure 90/70 mm. Hg. The heart was of normal size and the rate was regular; no murmurs were heard. The lungs were clear to auscultation and to percussion. The liver and spleen were not palpable. There was moderate generalized abdominal tenderness.

X-ray of the chest revealed a soft infiltration of the right first and second interspaces, and of the apical region without cavitation. A soft infiltration also was noted in the left first interspace. It was concluded that the findings were consistent with acid-fast lesions of the apices, predominantly in the right apex (Fig. 4).

Laboratory Tests.—Blood hemoglobin content was 10 Gm. per 100 ml., leukocyte count 4,500 per cubic millimeter, and erythrocyte count 3,780,000 per cubic millimeter. Urinary albumin test was plus 3, specific gravity 1.025, pH 5.0, and sugar and acetone tests were negative; there were a few granular casts and 3 to 5 pus cells per high-power field. Blood urea was 120 mg. per 100 ml., blood sugar 97 mg. per 100 ml., and serum proteins 4.7 Gm. per 100 ml. with albumin 1.5 and globulin 3.2 Gm. per 100 ml. Urine culture was positive for *Esch. coli*. Two gastric washings were negative for tuberculosis. An LE test was negative.

Course.—Because of the possibility that the apical lesions were of tuberculous origin, the patient was isolated and steroidal treatment was withheld. The gastric washings were negative for acid-fast bacilli. A tentative clinical diagnosis of systemic lupus erythematosus was made, and on January 24, five days after admission, cortisone therapy, 100 mg. daily, was begun. Twenty-

four hours later, the patient said she felt better. On January 23, after four days of cortisone therapy, the patient's general condition had improved. She appeared to be more alert, felt stronger, and had become more active. X-ray of the chest on January 30 revealed a slight increase in the infiltration of the left apex (Fig. 5). On February 2, two weeks after admission, an LE test was positive plus 1. An x-ray of the chest on February 14 revealed that the upper lung field had cleared (Fig. 6). Cortisone therapy was continued until the patient was discharged on Feb. 21, 1950. After discharge, the patient was maintained on 10 to 15 mg. of ACTH daily.



Figs. 4, 5, and 6.—Case 5. Roentgenograms of chest.

On March 7, two weeks after discharge, the blood urea had returned to a normal level of 21 mg. per 100 ml.

No further pulmonary lesions appeared, but a flare-up of the renal condition occurred on Oct. 17, 1950, eight months after discharge. The administration of cortisone, 100 mg. daily, without ACTH was resumed. The condition gradually improved and the patient continued to take cortisone. Findings on a follow-up examination on Feb. 21, 1951, approximately a year after initial admission, were essentially negative except for some pitting edema.

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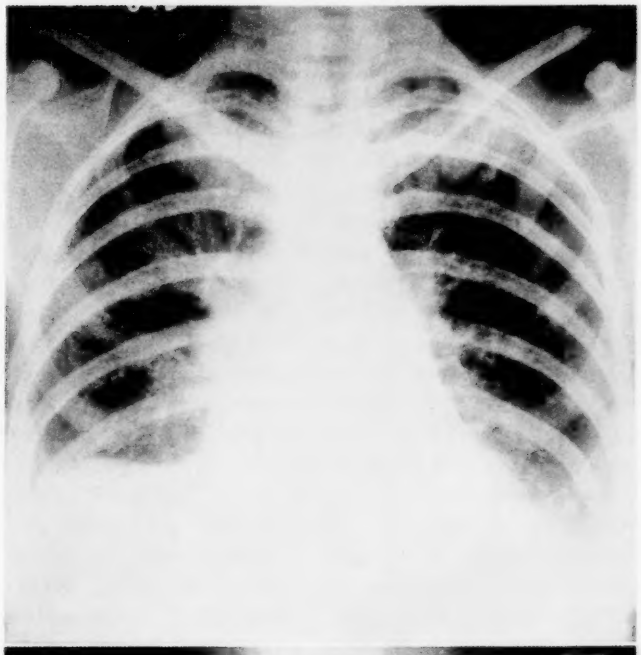

Fig. 5.

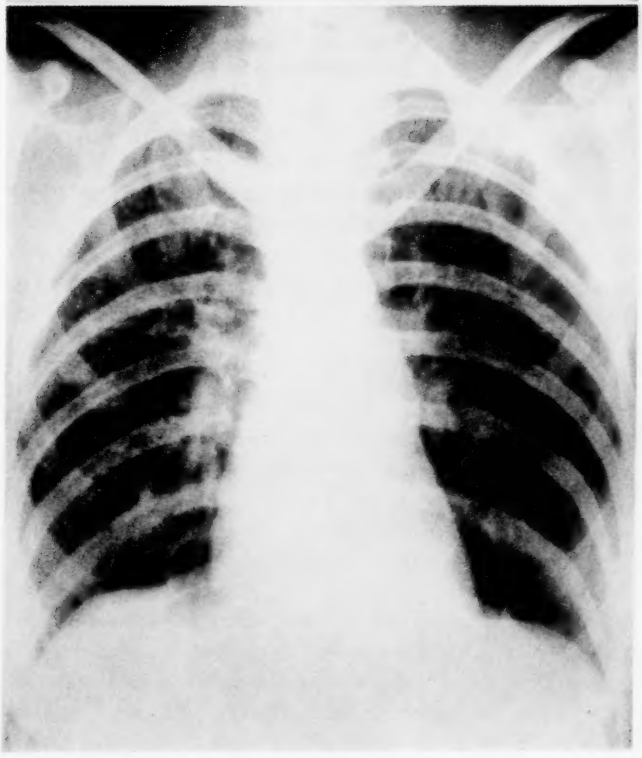

Fig. 6.

Figs. 5 and 6. *(For legends see opposite page.)*

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DISCUSSION

Recently, Purnell, Baggenstoss, and Olsen[7] discussed the various pathologic lesions that were discovered at autopsies of 54 patients having systemic lupus erythematosis. These were alveolar wall inflammation, focal and diffuse atelectasis, acute fibrinous pleuritis (42.6 per cent), acute purulent bronchitis, bronchopneumonia with alveolar septal organization, and, most prominently, mucinous edema of the alveolar walls, perivascular and peribronchiolar tissues. Griffith and Vural[9] correlated the clinicopathologic findings in 18 cases of SLE in their series wherein some degree of relationship existed between the clinical pulmonary manifestations and the pathologic changes in the lungs. No lesion pathognomonic of SLE has been found in the pulmonary parenchyma, although the basophilic mucinous edema in the connective tissue of the alveolar walls and in the perivascular and peribronchial tissues in the patients having SLE and interstitial pneumonitis, described by Purnell and associates,[7] may be considered a unique lesion. The possibility that that lesion is specific is especially interesting since, in the first 3 cases above described, no similar lesion in the pulmonary tissue could be demonstrated at necropsy. However, one case demonstrated a rather severe bronchiolitis and another revealed marked alveolar necrosis.

Allergic focal pneumonitis,[10] primary atelectasis,[2] and primary atelectatic pneumonitis—"giant cell type,"[11] each has been described in association with SLE. In a monograph on systemic lupus erythematosus, Marmont[12] states that the pulmonary pathologic changes are secondary to other changes and are of bronchopneumonic type. Tumulty[13] found that the changes in the hyaline membrane that occur in lupus pneumonitis and the metaplasia of the bronchiolar epithelium also can occur in systemic lupus erythematosus.

The bizarre pulmonary findings encountered in association with systemic lupus erythematosus may simulate tuberculosis, sarcoidosis, the pneumoconioses, viral pneumonias, mycotic infections, Hamman-Rich syndrome, and scleroderma. In Case 5 the pulmonary apical lesions simulated those of tuberculosis very closely and it was only after negative gastric washing and repeated positive LE tests had been obtained that the diagnosis of systemic lupus erythematosus was established.

The x-ray pattern of the lungs in systemic lupus erythematosus also is variable and can range from segmental focal involvement to diffuse, patchy dissemination. There are no areas of predilection inasmuch as basal and apical lesions have been observed equally often. Gould and Daves[8] demonstrated x-ray changes in the lungs in 50 of 100 patients having SLE: 78 per cent of these 50 patients had focal patchy changes; 22 per cent had linear areas of infiltration, and one patient had miliary lesions. In 41 of the 50 patients, the lesions were in the lower lobes.

The treatment for the pulmonic manifestations of systemic lupus erythematosus is indirect. Basically it is the treatment for the underlying disease. Steriod treatment is important, because, in conjunction with antibiotic therapy, it may be the potentiating factor in the clinical remission. Case 4 is an example of the relationship: there was a dramatic clearing of the pneumonia subsequent to superimposing cortisone therapy on penicillin therapy. Prior to the adminis-

tration of steroids, a six-day period of penicillin therapy had brought about no improvement. In Case 5, tuberculosis was simulated by the apical infiltrations.

The finding on necropsy of masses of fungi suggestive of the genus *Aspergillus* remains unexplained. Fungi were found in Patients 2 and 3, and only in the latter patient had steroids and also antibiotics been administered. In Patient 2, large doses of Benadryl had been given. Peabody[14] notes that such organisms can occur in the respiratory tract without being pathogenic.

SUMMARY

1. The pulmonic manifestations of systemic lupus erythematosis (SLE) can be the predominant clinical symptoms at any stage of the disease.

2. The pulmonary findings can be bizarre and can simulate a variety of respiratory lesions. Unexplained, chronic, pulmonary involvement should make the clinician suspect that systemic lupus erythematosus is the basic disease.

3. The most beneficial treatment of the pulmonary parenchymal lesion of SLE appears to be steroid therapy. Antibiotics used solely in two cases failed to alleviate the pulmonary pathologic process, but both patients improved after steroid treatment had been instituted.

4. The significance of fungi in the pulmonary parenchymal tissue at necropsy is not understood at present, because they are found under widely differing circumstances. Fungi were found in the pulmonary parenchymal tissue of one patient who died before steroids were available for therapy and in that of another patient who had received both steroids and antibiotics over a relatively long period of time.

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THE EPIDEMIOLOGY OF ATHEROSCLEROSIS AMONG A RANDOM SAMPLE OF CLOTHING WORKERS OF DIFFERENT ETHNIC ORIGINS IN NEW YORK CITY

I. Prevalence of Atherosclerosis and Some Associated Characteristics

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A NUMBER of favorable circumstances provided an unusual opportunity to undertake an epidemiologic study of atherosclerosis and related conditions among a population of employed clothing workers in New York City: (1) an essentially random sample of the population could be obtained, (2) the population consisted of two major ethnic groups, men and women of Italian and Jewish parentage, (3) the population was unusually stable and homogeneous and was largely composed of older persons so that atherosclerotic manifestations could be expected to occur with appreciable frequency. Data based on this population group are not, of course, representative of the country as a whole but are presented for eventual comparison with studies on other population segments in this and other countries, as well as for their own interest.

The frequency of various manifestations of atherosclerosis, blood pressure levels, diabetes, body build, and serum lipid patterns have been observed among the different ethnic subdivisions of this population. Correlations of these data with each other will be made in a subsequent paper.[1] Dietary studies on this group[2,3] and some preliminary findings[4-6] have been previously published.

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METHODS

The participants in this study were examined at the Research Department of the Sidney Hillman Health Center which was maintained as a separate unit from the clinic, with its own staff, office space and laboratory. Each examination included a detailed family and medical history, complete physical examination, 12-lead electrocardiogram, posteroanterior chest roentgenograms and lateral roentgenograms of the abdomen, and blood tests and urinalysis. All the data were recorded on specially printed sheets and subsequently transferred to McBee Keysort cards for coding and analysis.

Data on familial prevalence of cardiovascular disease based on family histories were analyzed but are not reported since the basic reliability of such information, at least in this population group, was considered doubtful. Medical histories included information on all past or present diseases.

Physical findings were all recorded on the examination sheet but only those relevant to the study were coded. Height was measured without shoes and weight in underclothes. The chest girth was measured with a steel tape pulled tight midway between inspiration and expiration at the mid-sternal level. Hair distribution was gauged on an arbitrary scale of 0 to 3 by roughly estimating the amount of hair in four areas: scalp, extremities, chest, and back. Corneal arcus was likewise graded on a similar scale. Retinal findings were recorded but not coded; the same applied to findings on tortuosity of temporal, brachial, and radial arteries. Blood pressures were measured by auscultation in the right arm with a mercury manometer, immediately after the patient reclined and again at the end of the examination some 15 minutes later; for diastolic levels, both the point of change in sound (fourth phase) and complete disappearance of sound (fifth phase) were recorded. Pressures were read to the nearest 5 mm.

The diagnosis of coronary artery disease was based on a documented history of myocardial infarction, on a history of angina pectoris,[7] or on characteristic electrocardiographic signs. Before any diagnosis of coronary disease was accepted as established, the evidence was carefully weighed by two or more qualified observers. The following electrocardiographic signs were considered characteristic of coronary disease: Q_1T_1 patterns, Q_3T_3 patterns with concomitant changes in Lead aV_f, abnormally wide and deep Q waves according to a modification of Barker's criteria[8] (Q being 20 per cent or more of QRS in Leads I and/or II, 30 per cent or more of QRS in Leads V_5 and/or V_6, or 50 per cent or more in Lead aV_f), widening of the QRS interval to 0.12 second or more in the absence of undue cardiac hypertrophy, or S-T elevations or depressions of 2 mm. or more in one or more leads, unaccounted for by left ventricular strain or digitalis.

Aortic calcifications were diagnosed from posteroanterior 6 ft. chest plates and lateral roentgenograms of the abdomen. A definite, crescentric shadow in the aortic knob was considered indicative of calcification in the thoracic aorta. Calcifications in the abdominal aorta were graded as follows: a single, linear streak, at least 1 cm. long (grade I), multiple streaks, in line or parallel, anteriorly or posteriorly (grade II), and large, confluent plaques outlining the aorta (grade III). We assured ourselves in a separate study[9] that shadows thus diagnosed

represented true intimal and usually well-advanced atheromata with calcification. The chest films were slightly overpenetrated in order to reveal calcifications more clearly and the abdominal films were taken with a Bucky grid, as previously described.[4] Calcifications in the femoral and tibial arteries were diagnosed from roentgenograms of the thighs and legs, externally rotated.

In the chemical determinations, total serum cholesterol was determined by the method of Abell and associates,[10] serum phospholipid by the method of Fiske and SubbaRow,[11] serum uric acid by the method of Newton,[12] and blood sugar by Benedict's method.[13] Examinations included hemoglobin determination, serologic tests for syphilis, and urinalysis.

DESCRIPTION OF POPULATION GROUPS

Selection of the Sample.—The population available for study comprised approximately 33,000 men and women employed in the men's clothing industry in New York City and belonging to a trade union, the Amalgamated Clothing Workers of America. Two-thirds of these men and women were aged 40 and over. Nearly all workers making men's clothes in New York City are members of this Union. Approximately one thousand of the members aged 40 and over in this population were sampled at random (Table I), by methods described in

TABLE I. COMPOSITION OF SAMPLE

AGE	MEN			WOMEN				
	ITALIAN	JEWISH	OTHER	ITALIAN		JEWISH		OTHER PROBANDS
				PROBANDS	WIVES	PROBANDS	WIVES	
40–44	27	39	7	21	14	5	15	21
45–49	21	30	8	35	22	13	19	18
50–54	43	33	10	45	26	13	43	12
55–59	58	89	16	40	26	9	41	15
60–64	55	94	23	40	12	13	28	9
65–69	22	61	10	17	4	1	10	1
70–74	5	18	4	—	—	—	2	—
75+	1	8	1	1	—	—	—	1
Total	232	372	79	199	104	54	158	77
Mean Age (Years)	56	58	58	55	53	53	55	51

detail in an appendix to this paper. The sampling plan ensured proportional representation of work shops and factories of different sizes and of the various trades in the Union (coatmakers, pantsmakers, vestmakers, cutters, shipping clerks, bushelmen). The different ethnic groups within the Union and the different types of work done (operating machines, hand sewing, pressing, cutting cloth, and shipping) were proportionally represented. Men and women thus chosen at random will be designated as "probands." The over-all response rate was 90 per cent (Table XVIII).

In the course of the work, after 277 probands had already been examined, it became apparent that there were considerably fewer Jewish than Italian women at work. In order to obtain a larger sample of Jewish women, it was decided at that point to examine also the wives of the Jewish probands. Wives of Italian probands were examined as well since the sample of women would otherwise have been unduly weighted with Jewish housewives (Table I). On the assumption that the choice of a mate within the same population is, by and large, uninfluenced by the variables studied, it was felt justifiable to consider wives also part of the sample. Unless stated otherwise the wives will therefore be combined with the female probands. The response rate among the wives was 84 per cent (Table XVIII).

Composition and Social Characteristics of Groups.—The participants in this study came from a population which was unusually homogeneous and stable in many respects, as compared with the diversity of groups found generally in New York City. The composition of the sample by age, sex, and ethnic group reflected the history of the Union which was largely founded by Jewish and, somewhat later, Italian immigrants (Table I). Also represented in the sample was a group of mixed ethnic origin, mostly Slav; some were Negroes. Findings concerning this latter group will be given in a separate section. Approximately 90 per cent of the men and 80 per cent of the women aged 50 and over, in either of the two main ethnic groups, were born in Europe and had lived in the United States for a period of 40 to 50 years. While the groups adhered in distinctive ways to their native customs, and their patterns of live bore some resemblance to their early origins, they had become "Americanized" in many respects. Most of the Italians came from Southern Italy while the Jews were of predominantly Eastern-European origin.

Changes from one industry to another are very unusual among older workers in this group. They have remained garment workers since the beginning of their careers and, within the industry, hardly if ever changed from one particular type of work (operating machines, pressing, handsewing, cutting cloth, shipping) to another. Most have continued to live in New York City since their arrival in this country or since birth. Income levels are closely comparable among the different groups except for the cutters, who are more highly paid and receive a fixed salary while the other workers are remunerated on a piece-rate basis, determined by Union contracts.

Although the sample included persons carrying out different types of operations, these occupational differences were not marked. We have not studied these apparently minor factors nor their effect on the workers' emotional traits, as determined by their individual personality structure and their social and ethnic environment. An attempt to link social and emotional factors with health and disease has been made by Simmons and Wolff[14] but requires further investigation.

Among the Italians, 94 per cent of the men and 92 per cent of the women were married; among the Jews, the corresponding figures were 95 and 81 per cent. Italians had more children than the Jews; the average number of children was 3.0 among the former and 2.3 among the latter.

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Physical Characteristics.—It is likely that the interaction of both inborn and environmental factors plays a role in the genesis of atherosclerosis We have attempted to get crude measures of some of these factors in order to compare our own groups with each other and with other populations.

Among predominantly environmental factors, those relating to dietary habits appear of particular importance to the problem of atherosclerosis. Among Italians and Jews in this population group, it was found that their dietary fat intake was closely similar, amounting to approximately 35 per cent of their total caloric intake. Jews, on the other hand, consumed somewhat more fat of animal origin than the Italians, the proportion of animal to total fat intake being 80 per cent among the former and 68 per cent among the latter.[3] The caloric content of the diet, as opposed to its composition, might likewise be linked with

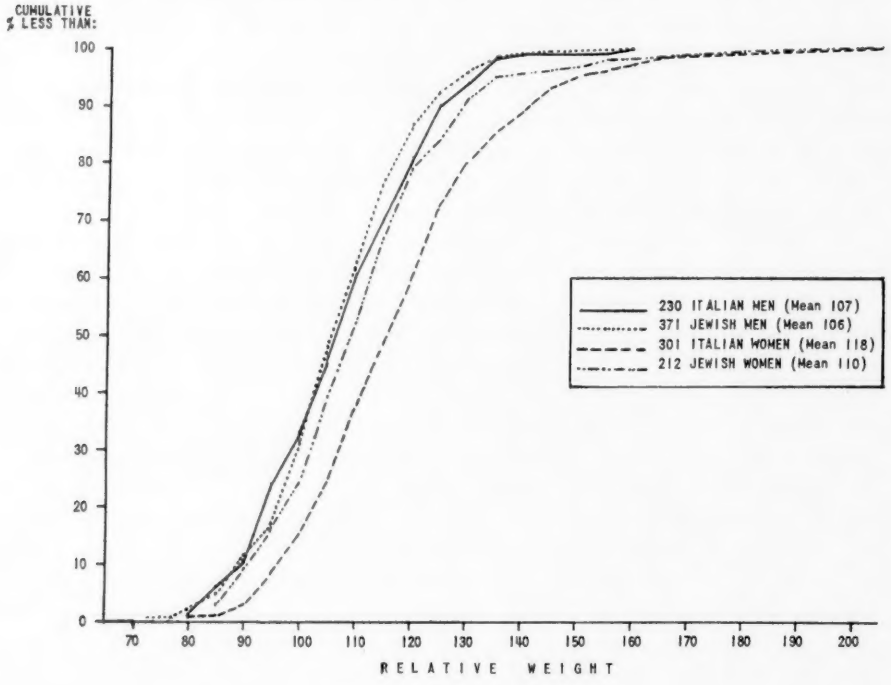

Fig. 1.—Relative weight.

the problem of atherogenesis. As previously discussed,[2] effects of caloric intake are best expressed in terms of relative weight rather than total daily food consumption. Our findings on relative weight are presented in some detail, not only because of their bearing on atherosclerosis but because of the relative scarcity of such data based on random population groups. Mean relative weights, expressed in terms of deviation from standard weight as determined from the Medico-actuarial tables,[15] were similar among Italian and Jewish men, while Italian women were appreciably heavier than Jewish women (Fig. 1). Mean relative weights showed no age trend in either sex or ethnic group. It is also apparent from these data that this population, as a group, was considerably

overweight, a fact which would have been accentuated by the use of standard weights at age 25.[16,17] Our choice of the older tables of standard weight has been previously explained.[3]

The men and women in these groups were of relatively short stature, mean height being 64 inches among the men and 60 inches among the women in both ethnic groups. Body configuration was roughly expressed in terms of the chest-girth-height ratio[18]; the shortcomings of this ratio were discussed in an earlier report.[2] The ratio may give a reasonable measure of the old subdivision into leptosomatic and pyknic builds. Sheldon's classification into "somatotypes"[10] has also been used for the purpose of defining a constitutional type prone to develop coronary heart disease.[20] The mean value of the chestgirth-height ratio was 0.56 among both Italian and Jewish men and 0.59 and 0.57 among Italian and Jewish women, respectively. This ratio is admittedly of limited value as an accurate measure of body build. It can, at least, be stated that in comparing Italians and Jews, we did not compare people of predominantly linear with others of mainly lateral build such as might occur with comparisons among other population groups.

Hormonal factors may be of considerable importance in coronary atherogenesis.[21-24] Inasmuch as hair distribution might afford some measure of "masculinity" we have studied this characteristic in a superficial way among our two main groups in order to get at least a rough indication of similarity or dissimilarity among Italian and Jewish men in this regard. There were no gross differences between these groups with reference to hair distribution. Baldness of the scalp (grades 0 and 1) was somewhat more common among the Jews in each decade and increased with age in either group, as expected. Italian men, on the other hand, showed slightly more hair on the chest and extremities in each decade while Jews were found to have a little more hair on the back.

"Hairiness" is more difficult to judge in women than in men and we are, therefore, not reporting our data on hair distribution in women. Since the age of onset of the menopause presumably reflects levels of estrogenic activity, it was of interest to find that Italian and Jewish women showed no differences in this regard. Of 160 Italian and 117 Jewish women aged 50 and over, excluding those in whom the menopause was artificially induced by operation, the mean age of onset of the menopause was 50 years in either group.

Since persons with coronary heart disease not infrequently show the presence of corneal arcus,[25] the frequency of the latter was determined (Table II). The frequency increased with age. There was no ethnic difference in the extent of the condition. Corneal arcus was observed less commonly in women than in men. Xanthelasma was, likewise, of comparable frequency among Italians and Jews (3 and 2.4 per cent, respectively, among men, and 2 and 2.4 per cent, respectively, among women). Xanthoma was found in but one woman in the entire sample.

Summarizing the present and preceding section, it may be stated that the Italian and Jewish men and women in this population were, by and large, similar in terms of the different variables mentioned; the relation of the latter to cardiovascular disease will be discussed subsequently.[1]

TABLE II. CORNEAL ARCUS

AGE	MEN				WOMEN			
	ITALIAN N = 231		JEWISH N = 372		ITALIAN N = 303		JEWISH N = 212	
	NUMBER	% OF TOTAL	Number	% OF TOTAL	NUMBER	% OF TOTAL	Number	% OF TOTAL
40–49	4	8	11	16	4	4	3	6
50–59	21	21	39	32	24	18	10	9
60–69	32	42	59	38	20	27	15	29
70–79	6	100	17	65	1	—	1	—
Total	63	27	126	34	49	16	29	14

General State of Health.—In return for their cooperation, participants were offered a complete examination. In fact, a considerable part of the time and effort spent on this study went into medical care, unrelated to the objects of research. Each participant was informed by personal letter of the result of the examination and many were referred to their private physician or to the various departments of the Sidney Hillman Health Center for further care. All important past or present illnesses, unconnected with the specific objectives of the study, were coded but no major effort was made to define criteria for these conditions with systematic accuracy.

The findings for Italian, Jewish, and other participants will be combined since there were, in general, no marked differences among them. About one-third of all the men but two-thirds of all the women had significant past or present illnesses (Table III). The difference could be accounted for by the fact that 19 per cent of the women had had major gynecologic operations and that gall-bladder disease and arthritis were more frequent among this sex. Most of the persons with gall-bladder, renal, and thyroid disease had had operations for these conditions. Pulmonary disease was mostly in the form of asthma or chronic bronchitis: a few persons gave a history of clinically significant tuberculosis. Serologic or unequivocal historical evidence of syphilitic infection was present among 1.5 per cent of the men and 1.2 per cent of the women.

PREVALENCE OF ATHEROSCLEROSIS

Coronary Heart Disease.—The frequency of coronary disease increased, as expected, with age among Italian and Jewish men. Coronary disease was more common among the Jews in each decade except in the forties where the number of diseased persons was too small for valid comparisons (Table IV). The overall frequency of coronary disease, adjusted to the age distribution of the total group of Italian and Jewish men, was 7.9 per cent among 232 Italian men and 15.8 per cent among 372 Jewish men ($P < 0.01$). Of the 78 Italian and Jewish men with coronary disease, 26 had been previously unrecognized.

TABLE III. PREVALENCE OF MAJOR NONCARDIAC DISEASES

	MEN N = 683 (PER CENT)	WOMEN N = 592 (PER CENT)
None	61	33
Arthritis	5	11
Renal disease	6	3
Gall-bladder disease	2	12
Peptic ulcer	6	2
Thyroid disease	1	3
Pulmonary disease	6	2
Neoplasms	1	1
"Nervous breakdowns"	2	2
Gynecologic operations	—	19
Prostatic disease	3	—

TABLE IV. PREVALENCE OF CORONARY HEART DISEASE

AGE	ITALIAN MEN N = 232		JEWISH MEN N = 372		ITALIAN WOMEN				JEWISH WOMEN			
					PROBANDS N = 199		WIVES N = 104		PROBANDS N = 54		WIVES N = 158	
	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL
40–49	2	4.2	2	2.9		—	1	2.8		—		—
50–59	5	5.0	17	13.9	3	3.5	4	7.7	1	4.6	2	2.4
60–69	9	11.7	32	20.6	3	5.2		—		—	5	12.5
70–79	1	16.7	10	38.4		—		—		—		—
Total	17	7.3	61	16.4	6	3.0	5	4.8	1	1.9	7	4.4
Adjusted to Age Distribution of Italians and Jews*		7.9		15.8		3.0		4.4		2.2		4.2
Adjusted to Age Distribution of all Men and Women		7.3		14.2		3.5†				3.5†		

*Adjustments made separately for men and women.
†Additional adjustments made for proportions of probands and wives.

Differences between Italian and Jewish men existed with regard to the clinical manifestations of coronary disease (Table V). Myocardial infarction, diagnosed from a history with or without residual electrocardiographic changes, occurred with significantly greater frequency among the Jews. Angina pectoris, in the absence of a history of infarction, also occurred more commonly among the Jews although the ethnic difference was less marked. Coronary disease diagnosed on the basis of electrocardiographic evidence alone showed no appreciable ethnic difference in frequency.

Frank electrocardiographic evidence of past infarction was, like its clinical counterpart, more often observed among Jewish than Italian men (Table VI); as expected, such patterns were sometimes seen in the absence of a clinical history of infarction. Bundle branch block and abnormal Q or T waves were also preponderant among the Jews but the ethnic difference was less marked.

TABLE V. PREVALENCE OF DIFFERENT MANIFESTATIONS OF CORONARY HEART DISEASE

	MEN				WOMEN			
	ITALIAN N = 232		JEWISH N = 372		ITALIAN N = 303		JEWISH N = 212	
	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL
1. Myocardial infarction (with or without 2 and 3)	2	0.9	21	5.7	2	0.7	2	0.9
2. Angina pectoris (with or without 3)	5	2.2	18	4.8	4	1.3	3	1.4
3. Electrocardiographic abnormalities (solitary)	10	4.3	22	5.9	5	1.6	3	1.4
Total	17	7.4	61	16.4	11	3.6	8	3.7

TABLE VI. PREVALENCE OF TYPES OF ELECTROCARDIOGRAPHIC ABNORMALITIES INDICATIVE OF CORONARY HEART DISEASE

	MEN				WOMEN			
	ITALIAN N = 232		JEWISH N = 372		ITALIAN N = 303		JEWISH N = 212	
	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL
Postinfarction patterns	2	0.9	16	4.3	—		2	0.9
Complete bundle branch block	4	1.7	14	3.8	4	1.3	1	0.5
Q or T wave abnormalities	4	1.7	12	3.2	2	0.7	1	0.5
Total	10	4.3	42	11.3	6	2.0	4	1.9

Since a relation between physical activity of work and coronary disease may exist,[26] it was of considerable interest to compare the prevalence of manifest coronary disease among the different occupational subgroups represented in the sample. Among Italian men, the prevalence of coronary disease among 98 machine operators was 7 per cent, among 70 handworkers 10 per cent, and among 57 pressers 5 per cent; there are very few Italian cutters and shipping clerks in this industry. Among Jewish men, the prevalence of coronary disease among 177 machine operators was 18 per cent, among 76 handworkers 20 per

cent, among 40 pressers 15 per cent, among 52 cutters 15 per cent, and among 26 shipping clerks who were, on an average six years younger, 4 per cent. The number of men in each of these occupational and ethnic subgroups was clearly too small to establish the relation, if any, between coronary disease and type of occupation in this industry. It seems justifiable to state, however, that coronary disease was approximately twice as frequent among Jews as among Italians, irrespective of type of work done, making it very unlikely that the over-all ethnic difference in coronary disease prevalence observed by us could have been attributable to some hidden occupational influence.

The prevalence of manifest coronary disease among women was lower than among men (Table IV). Female probands and wives are reported separately since it appeared that wives showed a higher prevalence than the probands in either ethnic group. It cannot be decided from these data whether working women (probands) with heart disease are less apt to remain employed, or whether housewives, as a group, are more prone to the development of coronary disease. When probands and wives were combined and the prevalence of coronary disease among them was adjusted to the age distribution of all the men and women and to the proportion of probands and wives, both Italian and Jewish women showed a prevalence of manifest coronary heart disease of 3.5 per cent (Table IV). It is thus apparent that the sex difference in the prevalence of coronary disease was higher in the Jews than in the Italians.

The different manifestations of coronary disease and the different types of electrocardiographic abnormalities among these groups of women showed likewise no consistent ethnic trends (Tables V and VI). The lack of any ethnic difference in the prevalence of coronary disease in women, as contrasted with men, is of interest and remains unexplained.

TABLE VII. PREVALANCE OF ROENTGENOGRAPHIC EVIDENCE OF AORTIC CALCIFICATIONS (THORACIC OR ABDOMINAL)

	MEN				WOMEN			
	ITALIAN N = 231		JEWISH N = 372		ITALIAN N = 302		JEWISH N = 210	
	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL
1. Thoracic aorta	9	3.9	20	4.6	16	6.2	11	5.6
2. Abdominal aorta	37	15.6	63	15.1	34	13.2	41	20.4
3. Both sites	14	5.6	22	3.9	12	4.7	16	8.9
Total (Adjusted to age distribution of all men and women)	60	25.1	105	23.6	62	24.1	68	34.9

Aortic Calcification.—We have considered roentgenographic evidence of aortic calcification a useful diagnostic sign of atherosclerosis in epidemiologic studies.[4,9] In a few cases, it is difficult to decide whether massive calcification is primarily medial or intimal in origin.[27] However, in the majority of cases

these aortic shadows undoubtedly indicate the presence of intimal and advanced atheromata with calcification.[9]

The prevalence of calcifications in the thoracic aorta showed no ethnic difference among the men or women (Table VII). Calcifications in the abdominal aorta or in both sites combined showed no ethnic difference among the men, while Jewish women seemed somewhat more commonly affected (Table VII). A similar picture emerged when the total prevalence of calcifications in either of the two or both sites was adjusted to the age distribution of all men and women (Table VII). As expected, the total frequency of roentgenographic signs of aortic calcification increased with age (Table VIII).

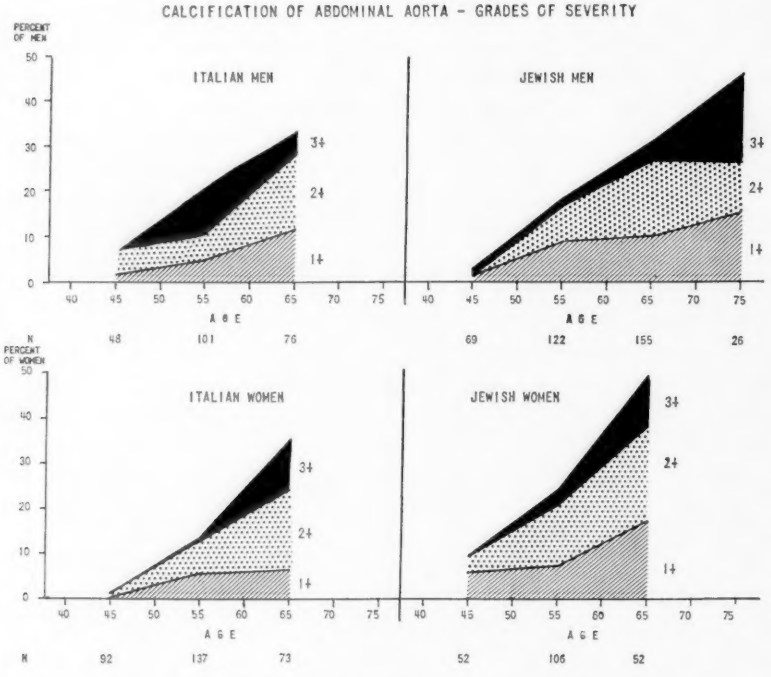

Fig. 2.—Calcification of abdominal aorta—grades of severity.

The severity of calcification in the abdominal aorta at different ages again showed no ethnic difference and was similar in the two sexes (Fig. 2). With advancing age, each grade of calcification increased in frequency but the relative proportions of the different grades showed no striking change with age. Strong, McGill, and Holman[28] have reached similar conclusions on the basis of extensive studies of aortic atherosclerosis from human autopsy material.

It is of interest that the sex difference observed for coronary disease did not apply for aortic disease and that, among men, the striking ethnic difference in the prevalence of coronary disease was likewise absent in the case of aortic disease. These findings lend additional support to an opinion previously expressed[4] that the factors which determine atherogenesis in man differ in the

aorta and the coronary arteries, an observation which has its counterpart in findings on cholesterol-fed, estrogen-treated chickens.[29]

Cerebral and Peripheral Artery Disease.—The presence of frank cerebrovascular disease would usually preclude industrial employment so that it was not expected that many individuals with this condition would be found in this sample. Among the total sample of 232 Italian and 372 Jewish men, one Italian and 3 Jewish men, all aged 60 and over, showed manifestations of cerebral artery disease. One Italian and one Jewish woman, out of a total of 303 and 211 women, respectively, had evidence of this condition.

TABLE VIII. PREVALENCE OF ROENTGENOGRAPHIC EVIDENCE OF AORTIC CALCIFICATIONS AT DIFFERENT AGES

AGE	MEN				WOMEN			
	ITALIAN N = 231		JEWISH N = 372		ITALIAN N = 302		JEWISH N = 210	
	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL
40–49	3	6.2	3	4.3	2	2.2	6	11.5
50–59	25	24.7	28	22.9	25	18.2	31	29.2
60–69	30	39.4	60	38.6	35	47.9	31	59.6
70–79	2	33.3	14	53.8	—		—	

Manifest peripheral artery disease appeared to be more common among Jews than Italians in either sex. The prevalence rates for this condition, adjusted to the age distribution of all the men and women, were 1.3 and 3.6 per cent, respectively, for Italian and Jewish men and 1.0 per cent for Jewish women; none of the Italian women were affected.

Among a smaller, consecutive sample of 73 men and 91 women, roentgenograms of the thighs and lower legs were taken in order to demonstrate calcifications in the femoral and tibial vessels; no persons with clinical manifestations of peripheral artery disease were encountered in this part of the sample. Arterial calcifications in one or both lower extremities were again more common among Jews than Italians in either sex (Table IX). The typical appearance of Mönckeberg's sclerosis was seen in the femoral vessels of only 4 of the men; in the remainder, the shadows were more patchy and suggestive or typical of atherosclerosis or a combination of intimal and medial lesions.

PREVALENCE OF HEART DISEASE OF ALL TYPES

In order to get a measure of the prevalence of heart disease of all types in the two main ethnic groups, the individuals with coronary disease (Table IV) were grouped with those showing hypertensive and rheumatic heart disease; also included are individuals in whom cardiac enlargement of undetermined etiology was the only manifest sign of heart disease (Table X). Hypertensive heart disease was diagnosed when (1) cardiac enlargement coexisted with hyper-

tension or left ventricular strain patterns or (2) when hypertension and left ventricular strain patterns occurred together. Hypertension was defined for this particular purpose as two systolic readings over 150 mm. Hg or one diastolic reading over 95 mm. Hg. Rheumatic heart disease was diagnosed according to accepted criteria.[30] Only one patient in the entire sample had syphilitic heart disease.

TABLE IX. ROENTGENOGRAPHIC EVIDENCE OF CALCIFICATION OF PERIPHERAL ARTERIES

ARTERY	MEN				WOMEN			
	ITALIAN N = 32		JEWISH N = 41		ITALIAN N = 57		JEWISH N = 34	
	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL	NUMBER	% OF TOTAL
Tibial	0	0	1	2.4	0	0	1	2.9
Femoral	3	9.4	10	24.4	2	3.5	2	5.9
Both sites	4	12.5	3	7.3	0	0	1	2.9
Total	7	21.9	14	34.1	2	3.5	4	11.8

TABLE X. PREVALENCE OF HEART DISEASES OF ALL TYPES

	MEN		WOMEN	
	ITALIAN N = 232 (PER CENT)	JEWISH N = 372 (PER CENT)	ITALIAN N = 303 (PER CENT)	JEWISH N = 212 (PER CENT)
Coronary heart disease	7.3	16.4	3.6	3.8
Hypertensive heart disease	5.2	7.8	7.9	4.2
Cardiac enlargement	3.0	3.2	5.9	1.9
Rheumatic heart disease	—	0.3	1.3	1.4
Total heart disease	15.5	27.7	18.7	11.3
Equivocal coronary heart disease	7.3	11.3	7.9	13.2

The total prevalence of manifest heart disease of all types was 15.5 per cent among the Italian and 27.7 per cent among the Jewish men; the corresponding figures for women were 18.7 and 11.3 per cent. The frequencies among the men, applying as they do to employed workers, and those among the women are of considerable magnitude.

In an additional group of individuals, the presence of coronary heart disease was suspected but not proved. Suspicion was based on history, electrocardiographic findings, or both. Altogether, some 7 to 8 per cent of the Italians and rather more than 10 per cent of the Jews in either sex showed equivocal evidence of coronary disease (Table X). In a minority of these, suspicion was based on an equivocal history of anginal pain. In the majority (about 90 per

cent of the Italians and 75 per cent of the Jews in either sex), suspicion was based on certain electrocardiographic abnormalities. Approximately half of the latter consisted of isolated T-wave inversions in Leads I, II, or over the left precordium, unaccounted for by left ventricular strain, or Q waves falling short of our established criteria but of sufficient depth to raise some doubt. The remaining half showed most often incomplete right bundle branch block, a finding of questionable significance, or, occasionally, S-T depressions or elevations between 1 and 2 mm.

BLOOD PRESSURE

The definition of "normal" blood pressure and its relation to age has been problematic for many years and has recently been re-evaluated.[31-33] Since our sample excluded younger people, our data did not lend themselves to an analysis of the usual course of blood pressure levels over the span of life. Our data, as reported, refer to a total population, including healthy people as well

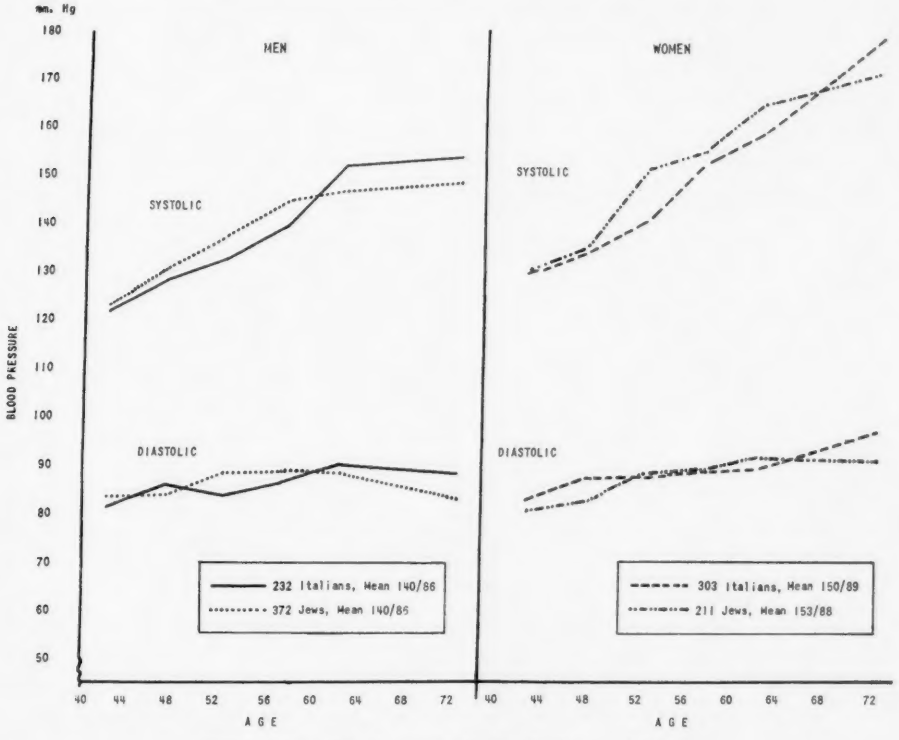

Fig. 3.—Mean blood pressure levels—Italians and Jews.

as sick persons whose illness did not prevent them from working and only few individuals in whom hypertension might have been secondary to renal or endocrine diseases.

In the analysis of the blood pressure trends to be reported here, the second blood pressure reading, as described under the section of methods, was used

throughout, being considered more basal. For systolic pressures, this reading was, on the average, some 4 mm. Hg lower than the first; the second diastolic reading was, on the average, about 1 mm. Hg lower than the first. The difference between the first and the second reading apparently did not show any relationship with age for either systolic or diastolic pressures. However, in the case of systolic pressure, the difference between the first and second readings was greater at initially higher blood pressure levels for both men and women. Systolic and diastolic pressures rose with age in both sexes and ethnic groups (Fig. 3). In the case of all the four groups, the upward trend in diastolic level was significant as evidenced by the fact that the mean pressure at age 40 to 44 years was significantly different at the 1 per cent level from that at age 60 to 64 years. The rise in systolic pressure with age was likewise significant.

In order to compare the blood pressure levels of the men and women in the two ethnic groups, the mean levels in these four groups were adjusted to the age distribution of all the men and women. Mean, age-adjusted systolic pressures among Italian men and women were 140 and 150 mm. Hg, respectively, and among Jewish men and women, 140 and 153 mm. Hg, respectively. Men differed from women in both ethnic groups at the 1 per cent level. The ethnic groups did not, however, significantly differ from each other. Mean, age-adjusted diastolic pressures were 86 mm. Hg among both Italian and Jewish men and about 88 mm. Hg among both Italian and Jewish women; the sex difference in diastolic level was not significant.

TABLE XI. MEAN BLOOD PRESSURE LEVELS FOR ALL MEN AND WOMEN

AGE	SYSTOLIC				DIASTOLIC	
	MEN		WOMEN		MEN	WOMEN
	N	MEAN B. P.	N	MEAN B. P.	MEAN B. P.	MEAN B. P.
40–44	66	123	55	130	82	82
45–49	51	130	89	135	85	85
50–54	76	135	126	145	86	88
55–59	148	143	116	153	88	88
60–64	149	149	93	161	89	90
65+	115	150	35	175	84	95
Total	605	141	514	148	86	88
Average S. D.		24		26	13	13

The combined data for Italians and Jews are given in Table XI. It is of interest that the mean systolic and diastolic levels at different ages were closely similar to those found by Pickering and associates[32] among an entirely different population. This finding would suggest that the determinants of blood pressure level are similarly distributed among some widely separated populations and that epidemiologic data might yield further valuable information.

Diastolic blood pressures as defined above referred to levels conventionally determined from change of sound (fourth phase). Levels estimated at the point of complete disappearance of sound (fifth phase) have been considered more indicative of true diastolic pressure, determined intra-arterially,[34,35] in spite of some disagreement on this issue.[36] Although fourth and fifth phase readings varied considerably in some instances, for the whole group the mean differences were slight, being approximately 3 mm. Hg for men and 2 mm. Hg for women, regardless of age. These data might be of value if a redefinition of "normal" diastolic blood pressure levels in terms of fifth rather than fourth phase readings should be contemplated.

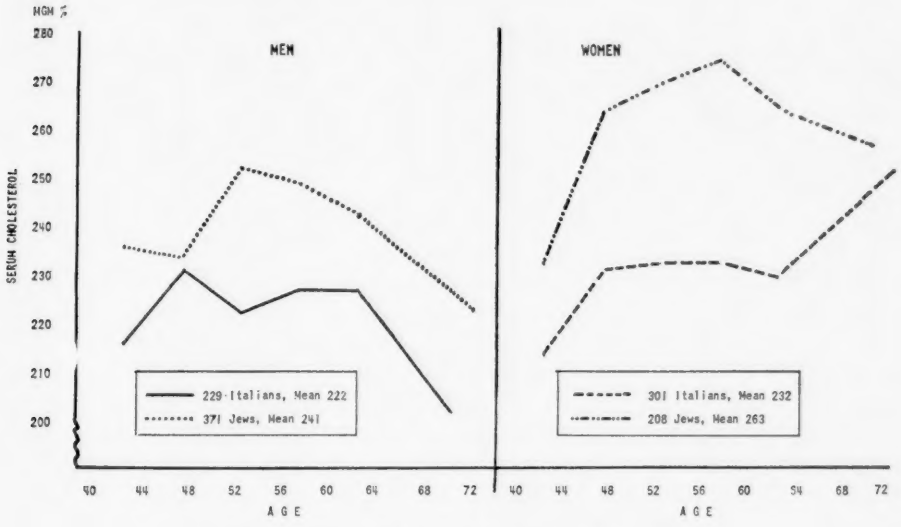

Fig. 4.—Mean serum cholesterol levels—Italians and Jews.

SERUM LIPID LEVELS

Serum lipid levels will be described with reference to the total population, irrespective of the presence or absence of diseases associated with serum lipid elevations; such data are best presented in this fashion.[37] The influence of serum lipid levels upon the diseases under investigation will be described in the second paper of this series.[1] Lipoprotein determinations were not made in these studies.

Total Serum Cholesterol.—Total serum cholesterol values were higher among Jews than Italians in each of the age groups and in either sex (Table XII; Fig. 4). The age-adjusted mean values were 222 and 241 mg. per cent among Italian and Jewish men, respectively, and 232 and 263 mg. per cent among Italian and Jewish women, respectively. Women showed significantly higher values than men regardless of ethnic group and Jews showed significantly higher values than Italians regardless of sex, at the 1 per cent level.

The age trends among both men and women appeared to be very difficult to interpret although certain of the obvious rises and falls could be shown to be

TABLE XII. MEAN SERUM CHOLESTEROL LEVELS—AGE, SEX, ETHNIC GROUP

AGE	MEN				WOMEN			
	ITALIAN		JEWISH		ITALIAN		JEWISH	
	N	MEAN CHOLEST.	N	MEAN CHOLEST.	N	MEAN CHOLEST.	N	MEAN CHOLEST.
40–44	27	215	39	235	35	213	20	233
45–49	21	231	30	234	57	231	30	264
50–54	42	222	33	252	70	232	56	269
55–59	58	227	88	249	66	232	48	274
60–64	55	227	94	243	52	229	41	265
65+	26	202	87	222	21	251	13	257
Total	229	222	371	239	301	230	208	264
S. D.		37		44		38		48
Adjusted to age distribution of all men and women		222		241		232		263

statistically significant. Among the men, these trends were in general accord with those described by Keys,[38] showing a rise of serum cholesterol levels into the fifties and a subsequent fall. Views on the relation between mean serum cholesterol levels and age, however, have not been entirely unanimous. Adlersberg and associates,[39] for instance, found no significant age trend beyond the thirties among men but, as in our series, serum cholesterol levels among women continued to rise beyond the fifties.

TABLE XIII. MEAN SERUM PHOSPHOLIPID LEVELS—AGE, SEX, ETHNIC GROUP

AGE	MEN				WOMEN			
	ITALIAN		JEWISH		ITALIAN		JEWISH	
	N	MEAN PHOSPH.	N	MEAN PHOSPH.	N	MEAN PHOSPH.	N	MEAN PHOSPH.
40–44	27	257	39	265	35	252	20	260
45–49	21	265	30	264	57	265	30	297
50–54	42	256	33	270	70	276	56	297
55–59	58	267	88	276	66	274	49	298
60–64	55	271	94	267	52	273	39	296
65+	26	248	87	247	21	297	13	291
Total	229	262	371	264	301	272	207	293
S. D.		39		42		37		42
Adjusted to age distribution of all men and women		262		266		274		292

Serum Phospholipid.—Serum phospholipid levels were similar among Italian and Jewish men, in contrast to serum cholesterol (Table XIII). Among women, however, as in the case of serum cholesterol, levels were significantly higher in Jews than Italians. Age trends for serum phospholipids were remarkably similar to the trends for cholesterol.

Cholesterol-Phospholipid Ratio.—The cholesterol-phospholipid ratio, as expected from the data on its constituent parts, was smaller in Italian than Jewish men; the respective age-adjusted means were 0.85 and 0.91. Though phospholipid levels were higher among Jewish than Italian women, cholesterol levels were even more elevated among the former so that the ratio, as among men, remained smaller among Italian than Jewish women; the age-adjusted respective means were 0.85 and 0.91. The ratio showed no sex difference within each ethnic group, unlike serum cholesterol or phospholipid levels alone. In view of the similarity in the age trends of serum cholesterol and phospholipid the ratio showed no appreciable change with age.

The cholesterol-phospholipid ratio has been said to be more constant from person to person than its constituent parts.[40] It has also been stated that the ratio tends to rise with increases in serum cholesterol[41]; our finding of a higher ratio among Jews is in accordance with this observation.

Uric Acid.—Serum uric acid levels, either alone or in combination with the cholesterol-phospholipid ratio, have been suggested as being helpful in distinguishing patients with coronary heart disease.[42] Serum uric acid levels have, therefore, been measured in this study. Uric acid levels showed no ethnic difference or age trend (Table XIV). However, men showed significantly higher levels than women in both ethnic groups. A sex difference in these levels has also been found in persons past the age of 65 by Gertler and Oppenheimer.[43]

TABLE XIV. MEAN SERUM URIC ACID LEVELS—AGE, SEX, ETHNIC GROUP

AGE	MEN				WOMEN			
	ITALIAN		JEWISH		ITALIAN		JEWISH	
	N	MEAN URIC ACID	N	MEAN URIC ACID	N	MEAN URIC ACID	N	MEAN URIC ACID
40–44	27	4.5	37	4.4	34	3.8	19	3.4
45–49	20	4.2	28	4.4	56	3.8	29	3.7
50–54	40	4.4	33	4.4	69	3.6	56	3.8
55–59	57	4.6	88	4.9	65	3.7	49	3.9
60–64	53	4.4	93	4.6	48	3.8	37	3.9
65+	26	4.7	86	4.6	21	4.0	13	4.3
Total	223	4.5	365	4.6	293	3.7	203	3.8
S. D.		1.0		1.0		0.8		0.8
Adjusted to age distribution of all men and women		4.5		4.6		3.8		3.9

PREVALENCE OF DIABETES MELLITUS

In view of the association between atherosclerosis and diabetes, a special effort was made to determine the frequency of the latter condition. Diabetes was diagnosed when there was (1) a verified history of prolonged glycosuria, treated by insulin or diet, or (2) evidence of definite hyperglycemia, with or without glycosuria, at the time of examination. Hyperglycemia was defined as follows: (1) fasting blood sugar levels exceeding 130 mg. per cent, (2) any level exceeding 200 mg. per cent, (3) levels exceeding 180 mg. per cent one hour, 150 mg. per cent 2 hours, or 130 mg. per cent 3 hours after the last meal. Most specimens were taken three or more hours after the last meal. The test was repeated if the level was only slightly in excess of 130 mg. per cent to exclude false positive diagnosis. Twenty-eight previously undiagnosed diabetics were discovered in the course of the work; 11 of these had both marked hyperglycemia and massive glycosuria.

The age-adjusted frequency of diabetes was similar among Italian and Jewish men (Table XV). Among the women, the frequency of diabetes was similar among Italian and Jewish probands (6.1 and 5.7 per cent, respectively) but higher among Jewish than Italian wives (11.8 and 7.9 per cent, respectively) so that the over-all frequency was higher among Jewish than Italian women. When these frequencies were adjusted, however, to the proportion of wives and probands in the sample and the age distribution of all men and women, no ethnic difference in the prevalence among women could be detected (Table XV). There was likewise no appreciable sex difference in the prevalence of diabetes.

TABLE XV. PREVALENCE OF DIABETES

AGE	MEN				WOMEN			
	ITALIAN N = 229		JEWISH N = 370		ITALIAN N = 301		JEWISH N = 207	
	N	% OF TOTAL	N	% OF TOTAL	N	% OF TOTAL	N	% OF TOTAL
40–49	1	2.1	1	1.5	1	1.1	2	4.0
50–59	6	6.1	13	10.7	9	6.6	13	12.6
60–69	10	13.0	12	7.7	10	13.9	6	11.5
70–79	—	—	4	15.4	—	—	—	—
Total	17	7.4	30	8.1	20	6.6	21	10.1
Adjusted to age distribution of all men and women		7.2		7.7		8.2*		8.7*

*Further adjusted to proportions of probands and wives.

FINDINGS AMONG A MIXED GROUP OF DIVERSE ETHNIC ORIGINS

The sample of the Union population included a number of workers (79 men and 77 women) of other than Italian and Jewish origin. While the number of persons involved is small, it seemed worth while to report some of the findings

as these might throw some light on the representativeness of the data regarding Italians and Jews. The majority of the workers in this group were either of Slav origin (44 men and 27 women) or Negroes (15 men and 22 women). In evaluating the data on women, their relatively younger age, as compared with Italians and Jews, must be taken into account.

The frequency of coronary disease among the men was closer to the corresponding Italian than to the Jewish rates (Table XVI). The frequencies of the other types of heart disease are also given. Roentgenographic evidence of aortic calcifications was more common among this group of men than among either Italians or Jews. Mean blood pressure levels were similar to those observed among Italians and Jews. Diabetes was less frequent in this group than in the two main ethnic groups. Serum cholesterol levels resembled, for women, those observed among the Italians; for men, levels were closer to those seen among the Jews but no significance can be attached to these similarities or differences in view of the inhomogeneities within this group and the small numbers involved.

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TABLE XVI. PREVALENCE OF ATHEROSCLEROSIS AND OTHER ATTRIBUTES AMONG A GROUP OF DIVERSE ETHNIC ORIGINS

	MEN	WOMEN
Total number	79	77
Mean age	58	51
Coronary heart disease	5.1%	1.3%
Aortic calcifications	39.1%	14.3%
Peripheral artery disease	1.3%	0
Diabetes	3.8%	5.3%
Hypertensive heart disease	7.6%	7.8%
Enlarged heart	2.5%	0
Rheumatic heart disease	0	1.3%
Mean blood pressure	148/89	143/86
Mean serum cholesterol	236	236
Mean height (inches)	66.4	61.7
Mean relative weight	104	112

FINDINGS AMONG A GROUP OF FAMILY MEMBERS

In addition to the random sample of workers some 500 of their family members were examined, including also younger individuals. The sample of family members, unlike the sample of probands, cannot be considered random inasmuch as no concerted effort was made to ensure cooperation of all available spouses, siblings and children of probands. Despite the selected nature of the sample, the trends for serum cholesterol conformed to those noted among the probands, levels being higher among Jews than Italians in either sex and higher among women in either ethnic group (Table XVII).

CONFIRMATORY MORBIDITY STUDIES AMONG DISABLED AND RETIRED WORKERS AND MORTALITY STUDIES AMONG ACTIVE WORKERS

The data relating to the higher frequency of manifest coronary heart disease among Jewish as compared with Italian men in this working population require

TABLE XVII. MEAN SERUM CHOLESTEROL LEVELS IN A GROUP OF FAMILY MEMBERS

AGE	MEN				WOMEN			
	ITALIAN		JEWISH		ITALIAN		JEWISH	
	N	MEAN CHOLEST.	N	MEAN CHOLEST.	N	MEAN CHOLEST.	N	MEAN CHOLEST.
<30	11	173	23	203	12	210	28	216
30–39	12	235	35	237	31	213	52	230
40–49	9	212	26	240	12	216	31	233
50–59	15	215	24	261	14	252	54	277
60–69	16	207	11	256	3	337	33	276
Total	63	209	119	237	72	226	198	249

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further critical evaluation. In particular, a serious limitation arises from the fact that our data refer to actively employed men. Italian men might be more prone than Jewish men to die immediately as the result of their first and unheralded attack of coronary thrombosis, or, having developed coronary heart disease, might be more prone than Jewish men to retire from work on account of the disease. Since only persons at work were available for sampling, such a situation would have resulted in a preferential withdrawal of Italian men with coronary disease and given rise to the fictitious impression that coronary disease was more common among the Jews.

In order to test these possibilities, we have made a supplementary study of morbidity rates among disabled and retired members and differential death rates among active members in either ethnic group. Since there were no ways of sampling disabled and retired workers, information concerning these groups had to be gathered from the files of the Amalgamated Life Insurance Company; mortality data among active members were also available from this source. All union members are enrolled in this company and, through it, are entitled to death, disability, retirement, and sickness benefits. We are indebted to Mr. James J. Shoaff, Executive Director of the company, for having permitted us to use these files.

The data on disabled men will be considered first. All men in this category are below age 65 since all members become eligible for retirement pension at that age. In order to qualify for a disability pension, a worker has to be declared "totally and permanently disabled" on the basis of an examination by a certified internist or cardiologist. Detailed reports of these examinations were available and carefully weighed by us. The records of all men who became disabled during the years 1952, 1953, and 1954 were examined. The ethnic origin of these men was determined from their names; in this population, names are almost invariably characteristic of the origin of their bearer. During the three-year period in question, 70 Italian and 85 Jewish men became permanently disabled. Of these, 21 Italians (30 per cent) and 37 Jews (44 per cent) either became incapacitated on account of coronary heart disease or, though

disability was granted for another illness, had manifestations of coronary disease which would have been considered diagnostic by the criteria stated for the main study. Thus, among disabled as among active men, coronary disease was more common among the Jews.

Is coronary disease also less frequent among Italian than Jewish men who retire on account of age rather than disability? Unfortunately, there was no way of obtaining information on morbidity among an unbiased sample of these men. It was necessary, therefore, to compute death rates for coronary heart disease and to assume these rates to parallel morbidity rates. Since death certificates supplied to insurance companies do not, in the state of New York, give causes of death, this information had to be collected from Amalgamated Life Insurance Company records pertaining to a city in a nearby state. The workers belonging to the Amalgamated Clothing Workers' Union in that city are closely similar, with regard to ethnic, occupational, and other groupings to the population studied in New York. In the three years 1952 to 1954, there were 239 Italian and 285 Jewish men on the retirement rolls, representing, respectively, 519 and 688 person years of retirement. Of these, 4 Italian and 15 Jewish men died of an unequivocal, acute coronary heart attack, according to photostatic copies of the original death certificates. Thus, the annual death rate from acute coronary disease among these retired men was 8 per 1,000 among Italian and 22 per 1,000 among Jewish men, again showing a preponderance of Jews over Italians with coronary disease.

Finally, we had to consider whether more Italians than Jews die of an acute coronary attack while actively employed. The data were again obtained from the same city in a neighboring state. The number of active union members in 1952, 1953, and 1954 was computed from knowledge of the active membership in 1955 in that city and of the number who died, retired, or enrolled during the preceding three years. The proportion of Italian and Jewish men among active workers was found from analysis of a random, 10 per cent sample of the total active membership. A critical evaluation of all deaths during these three years was again made from photostatic copies of the original death certificates; ethnic groups were determined from the names as well as the country of origin. The age-adjusted, annual rate for deaths from acute coronary heart attacks was found to be 2.7 per 1,000 among approximately 3,300 Italian but 4.1 per 1,000 among approximately 1,500 Jewish actively employed men.

In summary, analysis of the insurance data showed the following: (1) clinically manifest coronary disease was more common among Jewish men than Italian men who received disability pensions, (2) deaths from coronary heart disease were more common among Jewish than Italian men receiving "old-age" pensions, (3) deaths from coronary heart disease were more common among Jewish than Italian men "on the job." The uncertainities inherent in data based on records rather than direct examination would make it hazardous to attach undue importance to these statistics, were it not for the fact that the evidence points in the same direction in each of the three groups analyzed. Adding this evidence to the main body of data based on actual examinations of randomly chosen, active workers, there emerges a representative picture of

coronary heart disease prevalence among the total union population of active and retired men in the two ethnic groups. The conclusion appears warranted that coronary disease is, indeed, more common among Jewish than Italian men in this population.

DISCUSSION

Interest in the various epidemiologic aspects of atherosclerosis is not of recent origin; earlier findings have been reviewed[44-46] and critically examined.[47] It is apparent, however, that most of the questions investigated in these studies remained unanswered. The results were inconclusive because deductions were frequently made from data based on unrepresentative population samples or inadequate criteria for the diagnosis of arteriosclerosis. The importance of sampling and of using valid statistical methods of analysis has become recognized, but the clinical diagnosis of the various manifestations of atherosclerosis has remained a difficult and unsatisfactory task. *The Burden of Diseases*, the dramatically descriptive term used by Cohn and Lingg as the title of their monograph,[48] particularly the burden of arteriosclerotic heart disease, is largely unknown and demands investigation. A reasonable risk of working with methods of restricted accuracy must, therefore, be taken in this field.

It would be of great interest to make valid comparisons between our prevalence rates for coronary heart disease and those from the few other available studies based on representative population samples. Such comparisons are difficult since these studies differ from each other in one or more ways, e.g., diagnostic methods, age distribution, response rate, and others. Without going into detail, it may be said that the rates reported here for Italian men were roughly comparable with data based on two studies among civil servants,[49,50] a survey of Californian longshoremen,[51] and a study among medical practitioners in Great Britain.[52] On the other hand, rates as high or higher than observed among the Jewish men in the present study were found among residents in an urban area of Pittsburgh[53] and among active and retired Welsh coal miners.[54] Comprehensive morbidity data from five areas in the United States[55] are very difficult to compare with other findings, on account of differences in diagnostic methods. Results from another major study have not yet been reported.[56] The extensive studies of Morris and associates[26] are based on incidence rather than prevalence rates and are, therefore, not comparable to our data. In this connection, it is believed that prevalence rates, as applied to our particular problem, gave adequate and valid answers to the questions posed; no attempt will be made to discuss the relative merits of incidence as opposed to prevalence rates in general.

The data presented are not necessarily applicable to persons of Italian or Jewish extraction in general. In fact, it would be of special interest to compare the prevalence rates found by us with those among other groups of "Italian" and "Jewish" people in this country as well as in other parts of the world. Some studies of this kind have been carried out among Jews in Israel.[57,58] Only through such studies will it eventually be possible to segregate environmental from inborn factors in the genesis of atherosclerosis. Epidemiologic observations may contribute to this problem in two distinct ways. First, differences in disease

susceptibility, as demonstrated in the present paper, point to groups preferentially at risk. Second, such differences might be related to possible etiologic factors. The frequency of any such factors, as long as they are truly associated with atherosclerosis, would make each of these frequencies a partial measure of the predisposition toward atherosclerosis in the population under study. Our prevalence rates for serum lipid levels, blood pressure levels, overweight, and diabetes may now be viewed in this light.

The data on serum cholesterol levels are, in general, in keeping with those collected from different groups of people in the United States, mostly not chosen at random from their particular "universe." It is of interest that mean levels among older men in this country nevertheless resemble each other relatively closely, being somewhere between 220 and 250 mg. per cent. No attempt is made to review the extensive literature in support of this statement; the subject has been discussed by Keys and contrasted with results found in some other countries.[59] The serum cholesterol levels among the Jewish men in our sample may be thought to be particularly high. However, the mean levels are somewhat lower than those among a group of healthy Minnesotans in a different social group.[60] The levels among the Italian men, on the other hand, are in the lower range of values found in the United States but higher than those among Italian men in Italy.[61] Keys has suggested that the predisposition of a population toward the development of coronary heart disease may be related to serum cholesterol levels. This appears to be true when populations differing relatively widely in dietary fat intake and levels of serum cholesterol are concerned. The question arises how much of the difference in the prevalence of coronary disease found by us between Italian and Jewish men is accounted for by the relatively small difference in mean serum cholesterol levels; more epidemiologic studies are required to answer this question.

Our data on serum cholesterol levels among women are likewise in general accord with a number of other such studies; some of these have been reviewed.[62] Levels among older women tended to be higher than among men, as others have observed.[63] However, as far as the pathogenesis of coronary disease is concerned, it may be of greater significance that serum cholesterol levels are higher among men in the younger age groups.[39,64,65]

The similarity of our blood pressure levels and those found by Pickering and his group in England has already been pointed out. His data are also in basic agreement with extensive observations collected in this country by Master, Dublin, and Marks[66] and other studies, as reviewed by Hamilton, Pickering, Fraser Roberts, and Sowry.[32] Again, our experience seems to differ little from that of others in the Western hemisphere.

Comparison of our findings on relative weight with other observations is made difficult by the fact that the few studies which have been carried out differ in age distribution from ours and from one another with regard to the definition of standard weight; some of these data have been reviewed.[67] It would appear that between 20 and 30 per cent of men and women in this country are 10 or more per cent overweight while 7 to 15 per cent are 20 or more per cent overweight. In our group, about 40 per cent of the men were 10 or more per cent

above standard weight and 15 per cent were 20 or more per cent overweight. Women, particularly those of Italian extraction, showed an even higher prevalence of overweight.

For diabetes our prevalence rates in the sixth and seventh decades appear to be on the whole higher than the rates found at comparable ages in representative population samples in Oxford, Massachusetts,[68] and a Canadian community in Ontario.[69]

The population groups which were the subject of this study have been described in considerable detail with regard to their environment, physical characteristics, and state of health. The need to give all of this information arose from the fact that we do not know at the present time how many of the innumerable factors which constitute the internal and external environment of man are associated with atherosclerotic disease. In epidemiologic surveys, therefore, population groups should be described in terms of as many potentially relevant variables as feasible in order to control these variables when comparing different groups. Only in this way will it eventually be possible to separate relevant from irrelevant factors in the development of atherosclerosis. Atherosclerosis develops and grows against the background of the total environment of an individual or group. This environment includes, to mention but a few, genetic, dietary, social, and cultural factors as well as the diseases prevalent in the community. An attempt has here been made to describe the prevalence of atherosclerosis within a segment of the general population.

SUMMARY

The prevalence of manifest atherosclerosis and associated conditions has been studied among a working population who were members of a Union representing the workers in the men's clothing industry in New York City. Of the total Union population of 33,000 men and women, a sample of 683 men and 592 women aged 40 and over was drawn at random; an additional, nonrandom group of family members, including 183 men and 272 women, was also examined. The majority of the participants belonged to two different ethnic groups, and were first generation immigrants of Italian and Jewish origin; their social and economic status was otherwise comparable.

The prevalence of manifest atherosclerosis in this population was established on the basis of well-defined diagnostic criteria. Manifest coronary heart disease was twice as frequent among Jewish than among Italian men but no ethnic difference could be discerned among the women; the sex difference in prevalence was well marked. In contrast, aortic atherosclerosis, diagnosed on the basis of roentgenographic evidence of calcification in the thoracic and abdominal aorta, showed neither an ethnic nor a sex difference. Data on the prevalence of peripheral artery disease and calcifications in the arteries of the leg were also presented. Prevalence rates for hypertensive and rheumatic heart disease were also given.

The reported data include information on relative weight, height, and other bodily characteristics, blood pressure and serum lipid levels, the prevalence of

diabetes and the general state of health among this representative population sample and in the two main constituent ethnic groups.

Jewish men and women were shown to have higher serum cholesterol levels than their Italian counterparts but serum phospholipid levels were similar in the two ethnic groups. Serum uric acid levels were higher in men than in women but similar in Italians and Jews.

Systolic and diastolic blood pressure levels showed a rise with age but no ethnic difference.

No ethnic difference was demonstrated in the prevalence of diabetes mellitus.

An analysis of certain insurance records pertaining to this population group confirmed the evidence based on examination of the random population sample that coronary heart disease indeed occurred more commonly among Jewish than Italian men.

The study provides an example of a comprehensive epidemiologic study of manifest atherosclerosis and should establish a basis for comparison with other much-needed surveys of this kind.

The generous cooperation of Dr. Morris A. Brand, Medical Director of the Sidney Hillman Health Center in New York, was helpful to our work in many ways. Dr. Julian B. Hyman assisted with part of the medical examinations carried out in the course of the project. Mr. Moses Wurm and Mrs. Emily Nagler were responsible for the chemical determinations. Mrs. Edith Kleinberg helped with the statistical analyses.

APPENDIX AS TO SELECTION OF THE SAMPLE

One thousand men and women, aged 40 and over, actively employed in the men's clothing industry in New York City, were to be selected at random from the Union rolls. It was not possible, for a number of practical reasons, to sample from master lists of the total Union membership. Two files kept by the Union for collection of dues were used instead. The first file was subdivided into different "trades," according to the type of garment produced; for each of these, shops employing workers in the trade in question were listed by name and address. The second file contained lists of workers by name, sex, and social security number employed in each of these shops.

From the total number of workers employed in the different trades, the number of individuals needed in the sample from each of the trades was estimated.

Contact with the workers to be selected had to be through the shop. The primary sampling unit, therefore, was the shop. From the list of shops in each trade, a random sample was selected, using tables of random numbers. Since it was expected that several years would be required to complete the study, sampling of shops in each trade and, therefore, of workers in these shops was staggered over the three-year period required. The danger of losing individuals from the sample after selection was thus minimized.

Next, individuals in the shop were likewise sampled at random. The size of the shops varied from less than five to more than 500 workers. Practical considerations made it necessary to set up arbitrary limits for the number of individuals to be selected from a shop; these were: (1) the amount of time permitted by the shops for interviewing the workers and (2) the size of the available research staff. The number of individuals selected from shops of different sizes was as follows: 15 from shops employing 90 or more workers, 10 from shops employing 60 to 89, 7 from shops employing 30 to 59, 5 from shops employing 10 to 29, and 3 from shops employing less than 10 workers. The proportion of shops of different sizes was varied appropriately so that any given worker had approximately a constant chance to be selected regardless of the size of his shop. By using a table of random numbers, about twice as many individuals as needed were selected. These were checked in order of their random selection with a file containing ages. Random numbers referring to individuals under 40 years of age were discarded and replaced by the next random

number substituted until the exact number decided upon for that shop was secured. A record was kept of those discarded because of age.

After workers were selected, the shop was visited without delay because some workers move from shop to shop and because a shop may close down temporarily or permanently. Each worker selected was interviewed individually at a convenient time and those refusing to cooperate were patiently and sympathetically reassured. Readiness to meet on the spot all possible objections usually ensured cooperation; sometimes, the help of family members, the family physician, or a union representative had to be enlisted.

The rapport needed to make the workers feel comfortable was achieved in high degree by Mrs. Elizabeth Dunsay's friendliness, devotion, and ingenuity of approach.

The sampling of shops and individuals proceeded until the required numbers of workers within each type and size of shop was secured.

The over-all response rate was 90 per cent. A breakdown by sex and ethnic group is given in Table XVIII.

TABLE XVIII. RESPONSE OF RANDOMLY SELECTED MEMBERS AND WIVES

	ITALIAN		JEWISH		OTHER		TOTAL	
	SELECTED	% RESPONDED	SELECTED	% RESPONDED	SELECTED	% RESPONDED	SELECTED	% RESPONDED
Proband men	258	90	392	95	83	95	733	93
Proband women	229	87	58	93	83	94	370	89
Wives	146	78	189	89	—		335	84
Total	633	86	639	93	166	95	1438	90

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THE EPIDEMIOLOGY OF ATHEROSCLEROSIS AMONG A RANDOM SAMPLE OF CLOTHING WORKERS OF DIFFERENT ETHNIC ORIGINS IN NEW YORK CITY

II. Associations Between Manifest Atherosclerosis, Serum Lipid Levels, Blood Pressure, Overweight, and Some Other Variables

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WE HAVE previously described the prevalence of manifest coronary, aortic, and peripheral atherosclerosis among a random sample of working men and women, mostly of Italian and Jewish origin, employed in the clothing industry in New York City.[1] A number of factors which are thought to be relevant to the development of atherosclerosis were also assessed among this population group; in particular, serum lipid, blood pressure, and weight levels.

Associations between atherosclerotic manifestations, on the one hand, and variables such as serum lipid and blood pressure levels, on the other, are well known to exist. The strengths of these associations are, however, largely unknown since their estimation requires the collection of data based on unbiased population samples of healthy persons observed over prolonged periods of time in order to find the segments of the population from which the newly diseased persons came; i.e., a longitudinal study. The practical difficulties involved in conducting such investigations account for the fact that few studies of this kind have been made. In spite of the fact that our study was cross-sectional (i.e.,

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designed to determine prevalence rather than incidence), we hope to show that a number of valuable conclusions can be drawn from this type of survey. Evidently, the diversity of population groups, even within the same country, makes it impossible to gain a complete picture of the epidemiology of atherosclerosis from a single survey. Our particular study refers to a population of Italian and Jewish Americans who were actively employed at the time of sampling, to the exclusion of those who retired from work or became permanently disabled on account of disease.

In both prevalence and incidence studies the advantages of using random samples are counterbalanced to some extent by certain shortcomings. The relative infrequency of manifest atherosclerosis and elevated serum lipid, blood pressure, and weight levels among the general population results in a small yield of persons showing both disease and high levels of some of these atherogenic factors even though the original sample may be fairly large. Any attempt to correlate these variables will, therefore, suffer from an inadequacy in numbers which will also be reflected in our data. The limitations inherent in the diagnosis of atherosclerotic diseases have been stressed before[1] and obviously limit the validity of the data to be reported.

METHODS

The over-all design and methodology of the present study have been previously described.[1] Data on a dietary survey of this group have also been published.[2,3] In the present paper, an attempt will be made to relate manifest coronary heart disease, roentgenographic evidence of aortic calcification, peripheral artery disease, and diabetes mellitus with each other and with three factors known or suspected to be associated with these diseases, i.e., serum lipid levels, blood pressure levels, and relative weight. Since serum lipid and blood pressure levels both show age trends,[1] a method was used which permitted the allocation of an individual of any age group into "high," "intermediate," or "low" ranges of these variables. This was unnecessary in the case of relative weights which are, by definition, age-adjusted by being based on age-specific standard weights according to the Medico-Actuarial tables.[4]

In order to define age-specific "high," "intermediate," and "low" serum cholesterol levels, three corresponding percentile ranges were arbitrarily established as follows: (1) a "high range" including values above the ninetieth percentile point (i.e., the highest 10 per cent), (2) an "intermediate range" (i.e., the next 15 per cent), and (3) a "low range" including the lowest 75 per cent. In each five-year age group, the subjects were arranged in order of descending serum cholesterol values and the highest 10 per cent were taken as the "high range," the next 15 per cent as the "intermediate range," and the remainder as the "low range." In order to define these levels among the actual sample, all Italian and Jewish men were combined in one group and all Italian and Jewish women were combined in another. The serum cholesterol values characterizing the three levels in each quinquennium in either sex are given in Table I. Percentile ranges for "high," "intermediate," and "low" cholesterol-phospholipid ratios and serum uric acid levels were similarly determined. The

identical procedure was used for defining "high," "intermediate," and "low" diastolic blood pressure ranges (Table II).

In actual practice, it was not feasible to maintain the three ranges of "high," "intermediate," and "low," as described in the previous section, because the number of individuals above the ninetieth percentile point was too small for valid analysis. As a compromise, the frequency of coronary heart disease among individuals above the seventy-fifth percentile point ("upper range") was compared with the frequency found below that point ("lower range").

TABLE I. SERUM CHOLESTEROL PERCENTILE RANGES

AGE (YEARS)	MEN						WOMEN					
	HIGH RANGE*		INTERMEDIATE RANGE†		LOW RANGE‡		HIGH RANGE*		INTERMEDIATE RANGE†		LOW RANGE‡	
	NO.	MG. %	NO.	MG. %	NO.	MG. %	NO.	MG. %	NO.	MG. %	NO.	MG. %
40–44	6	Over 286	10	286–255	50	Under 255	5	Over 271	8	271–246	42	Under 246
45–49	5	Over 294	6	294–257	40	Under 257	8	Over 319	15	319–266	64	Under 266
50–54	8	Over 311	8	311–253	59	Under 253	13	Over 305	19	305–271	94	Under 271
55–59	16	Over 297	20	297–265	110	Under 265	11	Over 315	18	315–267	85	Under 267
60–64	15	Over 298	22	298–266	112	Under 266	9	Over 295	15	295–275	69	Under 275
65–69	8	Over 271	11	271–248	62	Under 248	3	Over 308	5	308–280	23	Under 280
70+	3	Over 264	5	264–236	24	Under 236		—		—		—

*Above 90th percentile point.
†Between 75th and 90th percentile points.
‡Below 75th percentile point.

TABLE II. DIASTOLIC BLOOD PRESSURE PERCENTILE RANGES

AGE	MEN						WOMEN					
	HIGH RANGE*		INTERMEDIATE RANGE*		LOW RANGE*		HIGH RANGE*		INTERMEDIATE RANGE*		LOW RANGE*	
	NO.	MM. HG	NO.	MM. HG	NO.	MM. HG	NO.	MM. HG	NO.	MM. HG	NO.	MM. HG
40–44	5	Over 90	10	90	49	Under 90	6	Over 90	6	90	43	Under 90
45–49	5	Over 100	8	100–90	38	Under 90	8	Over 100	11	100–95	70	Under 95
50–54	6	Over 100	14	100–95	56	Under 95	11	Over 100	19	100–95	97	Under 95
55–59	13	Over 100	29	100–95	105	Under 95	13	Over 105	14	105–100	89	Under 100
60–64	18	Over 100	23	100–95	107	Under 95	13	Over 100	12	100	68	Under 100
65–69	6	Over 100	9	100–95	68	Under 95	3	Over 110	10	110–100	19	Under 100
70+	5	Over 95	3	95	24	Under 95		—		—		—

*Ranges defined as in Table I.

THE INFLUENCE OF SERUM LIPID, BLOOD PRESSURE, AND WEIGHT LEVELS ON THE PREVALENCE OF MANIFEST ATHEROSCLEROSIS

Coronary Heart Disease.—The frequency of manifest coronary disease among Italian men was higher in the upper than in the lower range of either

TABLE III. CORONARY HEART DISEASE RELATED TO SERUM LIPID, BLOOD PRESSURE, AND RELATIVE WEIGHT LEVELS

VARIABLE		MEN						WOMEN					
		LOWER RANGE* (LOW IN ALL INDICATED VARIABLES)			UPPER RANGE† (ELEVATED IN AT LEAST ONE INDICATED VARIABLE)			LOWER RANGE* (LOW IN ALL INDICATED VARIABLES)			UPPER RANGE† (ELEVATED IN AT LEAST ONE INDICATED VARIABLE)		
		TOTAL	C.H.D.‡	% C.H.D.	TOTAL	C.H.D.	% C.H.D.	TOTAL	C.H.D.	% C.H.D.	TOTAL	C.H.D.	% C.H.D.
Serum cholesterol	Italian	197	13	6.6	32	4	12.5	253	9	3.6	47	2	4.3
	Jewish	260	41	15.8	111	20	18.0	124	5	4.0	82	3	3.7
Cholesterol-phospholipid ratio	Italian	193	14	7.3	36	3	8.3	248	8	3.2	52	3	5.8
	Jewish	262	37	14.1	109	24	22.0	130	5	3.8	74	3	4.1
Serum uric acid	Italian	178	11	6.2	45	5	11.1	226	10	4.4	66	1	1.5
	Jewish	276	48	17.4	89	13	14.6	146	6	4.1	55	2	3.6
Diastolic blood pressure	Italian	170	11	6.5	62	6	9.7	226	7	3.1	76	4	5.3
	Jewish	280	45	16.1	92	16	17.4	160	7	4.4	50	1	2.0
Relative weight	Italian	138	7	5.1	92	10	10.9	110	5	4.5	190	6	3.2
	Jewish	225	36	16.0	146	25	17.1	109	4	3.7	101	4	4.0
Cholesterol and diastolic blood pressure	Italian	146	8	5.5	83	9	10.8	194	5	2.6	106	6	5.7
	Jewish	192	31	16.1	179	30	16.8	96	4	4.2	110	4	3.6
Cholesterol, diastolic blood pressure and relative weight	Italian	101	3	3.0	127	14	11.0	70	3	4.3	228	8	3.5
	Jewish	126	18	14.3	244	43	17.6	50	1	2.0	156	7	4.5

*Below 75th percentile point.
†Above 75th percentile point.
‡C.H.D. Coronary heart disease.

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serum cholesterol, blood pressure, or weight values while none of these variables appreciably affected the disease frequency among the Jewish men (Table III, Fig. 1). It is further apparent from these data that the greater prevalence of coronary disease among Jewish as compared with Italian men, discussed previously,[1] was not accounted for by the fact that serum cholesterol values were generally higher among Jewish than among Italian men[1] since the frequency of manifest coronary disease was higher among Jews, regardless of serum cholesterol range.

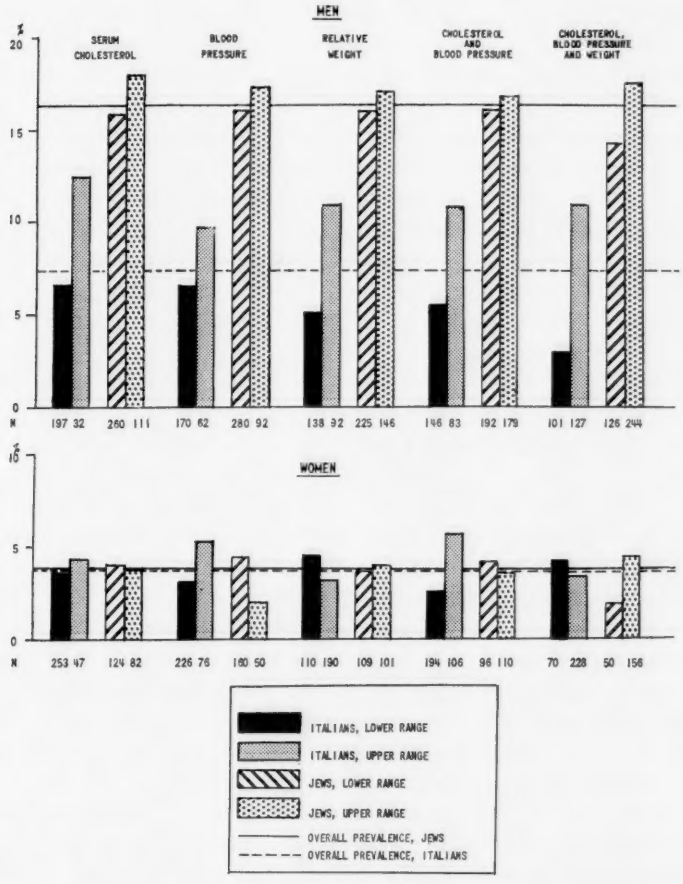

Fig. 1.—Coronary heart disease related to serum cholesterol, diastolic blood pressure, and weight levels.

On comparing the over-all prevalence of manifest coronary disease, 7.4 per cent among Italian and 16.4 per cent among Jewish men,[1] with the prevalence observed when both serum cholesterol and blood pressure levels were in the lower range or when all three variables (serum cholesterol, blood pressure, and weight) were in the lower range, frequencies were found to be only 5 and

3 per cent, respectively, among Italian men but remained essentially unchanged (16 and 14 per cent, respectively) among Jewish men (Table III, Fig. 1). It would, therefore, appear that the predisposition toward coronary disease observed among Jewish men may be largely due to an unknown factor unrelated to the three variables under discussion.

The cholesterol-phospholipid ratio differentiated Italian men with and without coronary disease less well than serum cholesterol level alone; among Jewish men, however, the ratio appeared to be more effective in this regard (Table III). Serum uric acid levels differentiated between men with and without coronary disease about as well as serum cholesterol levels alone (Table II).I

Among the women, as previously indicated,[1] no ethnic difference in the prevalence of coronary heart disease could be detected even though the ethnic difference in serum cholesterol levels was more marked than among the men.[1] Among the small number of women with coronary disease in the sample, it seemed that neither serum cholesterol, blood pressure nor weight levels consistently influenced the prevalence of this disease in either ethnic group (Table III, Fig. 1).

In evaluating the conclusions from this section, it must be emphasized that serum cholesterol, blood pressure, and weight levels were all determined after the onset of manifest coronary disease; a lowering in level of any of these variables after the event would have resulted in making their importance appear less evident from our calculations.

Aortic Atherosclerosis.—In addition to manifest coronary heart disease, the prevalence of manifest aortic atherosclerosis was studied from roentgenographic evidence of aortic calcifications which we believe to be indicative of generally advanced degrees of aortic intimal lesions.[5] Among Italian men, the prevalence of aortic calcifications seemed related to blood pressure and relative weight but not to serum cholesterol level; among Jewish men, aortic lesions were, if anything, less frequent at higher levels of blood pressure and relative weight while serum cholesterol level seemed to exert a slight enhancing effect (Fig. 2). On comparing the over-all prevalence of aortic calcifications (25.8 per cent among Italian and 28.3 per cent among Jewish men) with the prevalence observed when both serum cholesterol and blood pressure levels were low or when all three variables were in the lower range, frequencies were found to be appreciably less among Italian men while those among Jewish men, as in the case of coronary disease, remained essentially unchanged (Fig. 2).

Among the women, an association between aortic lesions and serum cholesterol and blood pressure level was evident in both ethnic groups while relative weight level exerted some influence only among those of Italian origin (Fig. 2). At low levels of both serum cholesterol and blood pressure, the frequency of aortic calcifications among Italian women was only 14 per cent, as compared with an over-all frequency of 20.5 per cent; among Jewish women, however, the frequency at low levels (29 per cent) was essentially the same as the over-all frequency (32.4 per cent) (Fig. 2). Similarly, when all three variables (serum cholesterol, blood pressure, and weight) were in the lower range, the frequency of aortic calcifications was only 11 per cent among Italian women but remained at 32 per cent among Jewish women. Thus, Italian women, like Italian men, seemed more sensitive than their Jewish counterparts to the enhancing effect of the three factors in question.

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THE INFLUENCE OF DIABETES ON THE PREVALENCE OF ATHEROSCLEROSIS

An association between atherosclerosis and diabetes has been established beyond doubt on the basis of extensive studies, as reviewed by LeCompte.[6]

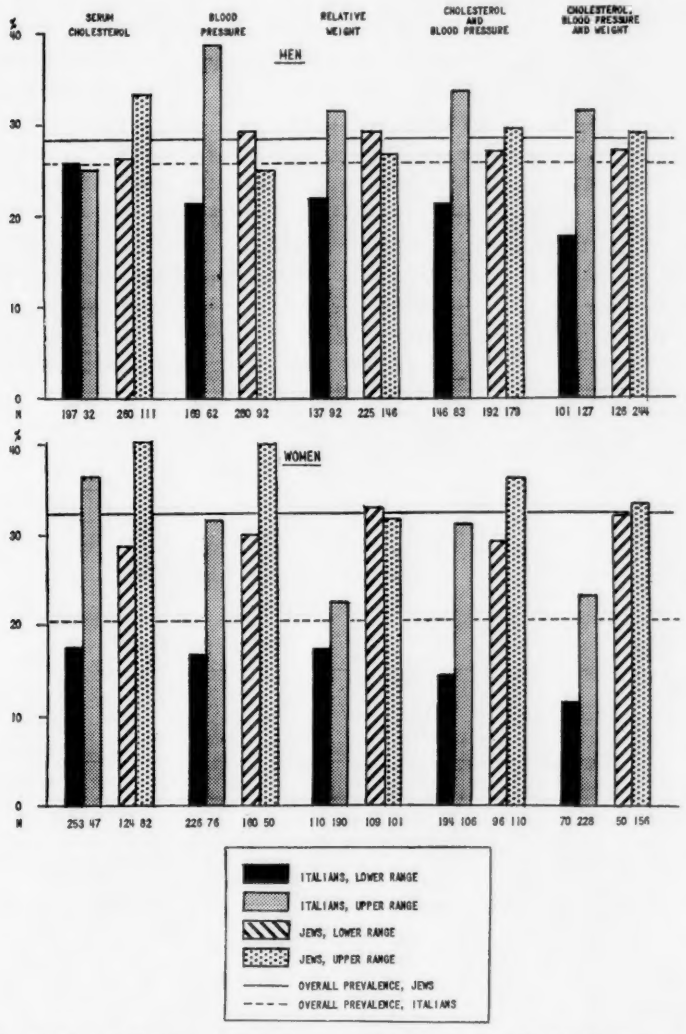

Fig. 2.—Aortic calcification related to serum cholesterol, diastolic blood pressure, and relative weight levels.

On the other hand, as Liebow, Hellerstein, and Miller[7] point out, this belief is almost entirely based on the comparison of autopsy material; their own study, based on a clinic population, also suffers from certain limitations which they discuss.

The advantage of our data, being based on an essentially random sample of a selected population, is counterbalanced by an inadequacy in numbers of diseased individuals. The number of persons with manifest coronary disease was small, and the number of those who had diabetes, in addition, was even smaller. In fact, only 1 Italian man and 6 Jewish men, out of 17 Italian and 30 Jewish male diabetics, showed evidence of coronary disease. Taking the data at their face value, coronary disease was no more frequent among diabetics than among nondiabetics (Table IV). These data do not, of course, negate the existence of a correlation between diabetes and coronary disease; the frequencies given are based on insufficient numbers and, moreover, the possibility exists that men who suffer from both diabetes and coronary disease are less prone to remain employed than men with only one of these conditions. In the case of aortic calcifications, however, a significant relation between this condition and diabetes was clearly demonstrated; half the diabetic but only a quarter of the nondiabetic men showed such calcifications (Table IV).

TABLE IV

DIABETES MELLITUS RELATED TO CORONARY HEART DISEASE

	WITH DIABETES			WITHOUT DIABETES		
	NO.	C.H.D.*	% C.H.D.	NO.	C.H.D.	% C.H.D.
Italian men	17	1	5.9	212	16	7.5
Jewish men	30	6	20.0	340	55	16.2
Italian women	20	2	10.0	280	9	3.2
Jewish women	21	1	4.8	184	7	3.8

DIABETES MELLITUS RELATED TO CALCIFICATION OF THE AORTA

	WITH DIABETES			WITHOUT DIABETES		
	NO.	CALCIF.	% CALCIF.	NO.	CALCIF.	% CALCIF.
Italian men	16	8	50.0	212	52	24.5
Jewish men	30	15	50.0	340	90	26.5
Italian women	20	12	60.0	280	49	17.5
Jewish women	21	10	47.6	184	58	31.5

*C.H.D. = Coronary Heart Disease.

Among 41 diabetic women in both ethnic groups, 3 (7 per cent) showed evidence of coronary disease; among 464 nondiabetic women, 16 (3 per cent) showed similar evidence. Aortic calcifications were significantly more frequent among diabetic women (Table IV).

TABLE V

AORTIC CALCIFICATION RELATED TO CORONARY HEART DISEASE

	WITH CORONARY DISEASE			WITHOUT CORONARY DISEASE		
	TOTAL	AORTIC CALCIF.	% CALC.	TOTAL	AORTIC CALCIF.	% CALC.
Italian men	17	8	47.0	214	52	24.3
Jewish men	61	26	42.6	311	79	25.4
Italian women	11	8	72.7	291	54	18.6
Jewish women	8	3	37.5	202	65	32.2

PERIPHERAL ARTERY DISEASE RELATED TO CORONARY HEART DISEASE

	WITH CORONARY DISEASE			WITHOUT CORONARY DISEASE		
	TOTAL	PERIPH. ART. DIS.	% P.A.D.	TOTAL	PERIPH. ART. DIS.	% P.A.D.
Italian men*	17	1	5.9	214	2	0.9
Jewish men*	61	6	9.8	311	11	3.5

*Peripheral artery disease was found among only 2 women.

RELATION OF CORONARY HEART DISEASE TO OTHER MANIFESTATIONS OF ATHEROSCLEROSIS AND MISCELLANEOUS CONDITIONS

It is well known from pathologic experience that the term "generalized arteriosclerosis" is frequently unjustified. In the same person, extensive aortic atherosclerosis may coexist with slight coronary artery involvement or the reverse situation may be encountered; moreover, coronary occlusion may occur in the absence of extensive coronary disease. Such findings do not preclude that, in a statistical sense, persons with advanced disease in one arterial bed also tend to show advanced lesions in other arteries. From our data, based on clinical rather than pathologic evidence of atherosclerosis, this would seem to be the case. Men with manifest coronary heart disease showed roentgenographic evidence of aortic calcifications more commonly than those without (Table V); it is of interest that there was no ethnic difference in this regard. A similar trend, based on insufficient numbers, was found among Italian but not among Jewish women (Table V). Peripheral arterial disease also occurred more commonly among men with than without coronary disease or aortic calcifications (Table V); the numbers involved were small.

In the preceding sections, the prevalence of coronary heart disease has been related to serum lipid, blood pressure, and weight levels and to the frequency of diabetes mellitus. In addition, we have obtained data on some other possibly

relevant factors. These data have been summarized in an attempt to delineate a "profile" which might differentiate men with manifest coronary heart disease from unaffected men (Table VI); there were too few women with coronary disease for a similar analysis. Serum lipid and blood pressure values have been expressed in terms of mean values rather than percentile levels; details relating

TABLE VI. PROFILE

	ITALIAN MEN		JEWISH MEN	
	WITH CORONARY DISEASE	WITHOUT CORONARY DISEASE	WITH CORONARY DISEASE	WITHOUT CORONARY DISEASE
Total Number	17	215	61	311
Age				
Mean	59	56	62	58
Born in United States	0	14.4%	9.8%	12.9%
Years in United States				
Mean	43.3	40.6	45.0	36.3
Number of Children				
Mean	2.9	2.7	2.6	2.3
Marital Status				
Single	11.8%	5.6%	0	6.1%
Height (inches)				
Mean	63.0	64.2	64.0	64.3
Dietary Fat Intake				
40% or more of total calories	25.0%	22.0%	22.2%	18.6%
Overweight				
Relative weight over 120	29.4%	18.8%	4.9%	14.8%
Body Build				
Chestgirth-Height ratio 6.0 and over	23.5%	24.1%	19.7%	20.3%
Hair Distribution				
Marked baldness of scalp (grade 1)	17.6%	20.3%	27.9%	25.5%
Blood Pressure (mm. Hg)				
Mean Systolic	155	139	147	141
Mean Diastolic	91	86	87	86
Serum Cholesterol (mg. %)				
Mean	235	221	241	238
Cholesterol-Phospholipid Ratio				
Mean	0.85	0.85	0.91	0.90
Serum Uric Acid (mg. %)				
Mean	4.8	4.4	4.5	4.6
Corneal Arcus				
Prevalence	41.2%	26.2%	44.3%	32.0%
Diabetes Mellitus				
Prevalance	5.9%	7.5%	9.8%	7.8%

to other items used in the "profile" were given in the preceding paper.[1] Men with and without coronary disease evidently were quite similar with regard to age, body build, and data relating to their personal history. Serum lipid and blood pressure levels conformed with the conclusions already made on the basis of percentile ranges of these variables. Jewish men showed somewhat more baldness of the scalp but there was no difference between those with and without coronary disease; body hair distribution was likewise not different in the latter two groups. Corneal arcus, as previously reported,[8] occurred slightly more

commonly among men with coronary disease. The "profile" among the men certainly would not suggest that those with manifest coronary disease differed in any gross fashion from unaffected individuals within the same population group, an impression long gained from clinical experience.

DISCUSSION

Inability to explain the predisposition of Jewish men toward the development of coronary heart disease on the basis of their tendency toward higher cholesterol levels, as compared with Italian men, appears to be one of the most interesting findings from the present studies. Kendall,[9] summarizing present knowledge concerning the relationship between atherosclerosis and serum lipids, has stated that elevated levels of certain serum lipids appear to be a factor in the development of intimal lesions in normal arteries, while much lower levels may be associated with lesions in vessels previously damaged. Seen in this light, there might be unknown factors which predispose the arteries of Jewish men toward the deposition of serum lipids. Such previous damage could play a role in explaining the higher prevalence of coronary disease among Jewish men in this population group.

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The data presented in no way contradict the general thesis elaborated by Keys[10] that serum cholesterol levels provide a measure of the predisposition of population groups toward the development of atherosclerosis in general, inasmuch as the two main groups did not differ in average serum cholesterol level to the same extent as the populations described by Keys. Our data merely indicate that population groups may be found which differ only slightly in serum cholesterol level and yet show striking differences in the prevalence of manifest coronary heart disease which appear to be independent of serum lipid levels as expressed in terms of total serum cholesterol.

In evaluating these data, it must be kept in mind that the men with coronary disease we have described tended to show serum cholesterol levels which were lower than some of the mean values reported for such patients in the literature. Moreover, men with a history of myocardial infarction seemed to have somewhat higher serum cholesterol levels than those with other manifestations of coronary heart disease; a similar relation was noted by Doyle and associates[11] in a preliminary communication. In patients with coronary disease, serum cholesterol levels higher than reported in this study were observed by a number of authors[12-17]; other data are more in line with our findings.[18-22] Some of these data have been reviewed by Katz and Stamler.[23] These differences are no doubt explained in part by differences in technique or by factors of selection in the choice of patients; partly, however, they may reflect variations between different groups of people in the reaction of their coronary vessels to the damaging effects of serum lipid constituents.

The present data have eliminated serum lipid levels, hypertension, obesity, or diabetes mellitus as accounting entirely for the demonstrated ethnic difference in coronary disease prevalence. Italians and Jews were well matched with regard to socioeconomic status and the type of work done.[1] In a previous publication, it was shown that caloric intake and the total fat consumption among

these Italian and Jewish populations were closely similar so that these dietary factors could also be largely excluded as a possible cause for the difference in coronary disease prevalence.[2,3] The proportion of animal and vegetable fat, however, differed among Italians and Jews; among the former, 32 per cent of the total fat intake was in the form of vegetable fat, among the latter, the corresponding figure was 20 per cent.[3] It was pointed out that the type of fat ingested might be important, particularly the degree of unsaturation of dietary fatty acids. Evidence has since accumulated that serum cholesterol levels are indeed influenced by these factors.[24-26] The slightly higher serum cholesterol levels observed among Jews in this population may in some part be due to their greater consumption of animal fats which are, in general, more saturated. We have, however, demonstrated that Jewish men showed more coronary heart disease than Italian men even at relatively low levels of serum cholesterol. The conclusion appears inescapable that diet or serum cholesterol level are not the only factors which predisposed these Jewish men toward the development of coronary heart disease.

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SUMMARY

The prevalence of various manifestations of atherosclerosis was measured among a random sample of clothing workers, aged 40 and over, of Italian and Jewish extraction, who were comparable with regard to working conditions, socioeconomic status, and dietary intake of calories and fat.

The over-all prevalence rate of coronary heart disease among Italian men appeared to be influenced by serum cholesterol, blood pressure, and body weight levels since the frequency of the disease was consistently greater at higher than at lower levels of these three variables. By contrast, among Jewish men who, as a group, showed evidence of coronary disease more frequently than Italian men, these variables exerted no appreciable effect upon the prevalence of the disease. The sample included too few women with coronary disease for a similar analysis. The prevalence of roentgenographic evidence of aortic calcifications appeared similarly more susceptible to the influence of the three variables in question among Italians than Jews in both sexes. Data relating the prevalence of manifest atherosclerosis to the serum cholesterol-phospholipid ratio and serum acid levels were also presented.

Aortic calcifications were more commonly seen in the presence than in the absence of manifest coronary disease; further interrelations between manifest coronary, aortic and peripheral arterial disease were also made. Comparison of Italian and Jewish men with and without coronary disease in terms of some more obvious possible atherogenic factors failed to delineate a "profile" which might help in characterizing the affected men.

These findings indicated primarily that the predisposition to the development of coronary heart disease of Jewish, as compared with Italian, men in this population segment is largely unexplained by any of the factors studied in these investigations. Presently undefined factors appear to be of considerable quantitative importance in determining the prevalence of coronary disease among certain predisposed groups and require further study, particularly by epidemiologic methods.

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CLASSIFICATION OF DISABILITY IN THE CHRONICALLY ILL AND AGING

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THE increasing number of chronically ill and aging persons has emphasized the need for an effective method to evaluate and classify their functional capacity. At present, medical diagnoses are the primary source of this information. These have been found to be inadequate, particularly when multiple medical and paramedical personnel are engaged in the interpretation of diagnostic terms. Stinson[1] and others have called attention to this deficiency in the case records. The National Conference on the Care of the Long-Term Patient, in its summary report, recommended the introduction of a simple and effective inter-agency referral system.[2]

The problem was recently highlighted by a rehabilitation survey of the residents in the Westchester County Home in Hawthorne, New York. The study was initiated to evaluate and determine rehabilitation potential. Extensive hospital charts were available, providing documented medical case records, but not any accurate data concerning the ability of the individual to function in his environment. Physical restoration and rehabilitation in this group of individuals emphasized the need for an effective method of functional classification based on age of the individual and his performance in the sheltered environment of the Home.

In a survey of 95 custodial patients in a municipal hospital, Dacso and his colleagues[3] based functional evaluation on mobility, utilizing various categories ranging from bedfast to wheelchair and ambulatory. In contrast, McBride[4] has set up rigid performance tests, based upon various occupational pursuits. He rates anatomic deficiency at 25 per cent of total disability, as compared with 75 per cent for functional deficiency. This ratio might well be applied to the chronically ill and aging.

In an attempt to reconcile these various performance criteria, we employed a systemic functional classification, based on the "Pulhems Profile" method developed by the Canadian Army and subsequently adopted by the U. S. Army during World War II.[5,6] In their original application, these systems were based on high rigid functional standards geared to the performance level of young men. It was necessary to change the specifications, and to include an additional category, namely, bowel and bladder continence, in order to apply the Profile

system to the chronically ill and aged. The numerical grades (of the "Pulhems Profile") 1 through 4 were maintained. Our work sheet explaining the various letters and grades employed is shown in Table I. This profile, as applied to chronically ill and aging persons, is really a performance test of the individual in a restricted environment with limited physical requirements. Its completion requires an examination of the patient by a physician with full access to all pertinent medical information and social data.

TABLE I. PHYSICAL PROFILE

P. *Physical* condition including diseases of the viscera (cardiovascular, pulmonary, gastrointestinal, urologic, and endocrine) and cerebral disorders which are not enumerated in the lettered categories below.
1. No gross abnormalities considering the age of the individual.
2. Minor abnormalities not requiring frequent medical or nursing supervision.
3. Moderately severe abnormalities requiring frequent medical or nursing supervision yet still permitting ambulation.
4. Severe abnormalities requiring constant medical or nursing supervision confining individual to bed or wheelchair.

U. *Upper* extremities including shoulder girdle, cervical and upper dorsal spine.
1. No gross abnormalities considering the age of the individual.
2. Minor abnormalities with fairly good range of motion and function.
3. Moderately severe abnormalities but permitting the performance of daily needs to a limited extent.
4. Severe abnormalities requiring constant nursing care.

L. *Lower* extremities including the pelvis, lower dorsal and lumbosacral spine.
1. No gross abnormalities considering the age of the individual.
2. Minor abnormalities with fairly good range of motion and function.
3. Moderately severe abnormalities permitting limited ambulation.
4. Severe abnormalities confining the individual to bed or wheelchair.

S. *Sensory* components relating to speech, vision, and hearing.
1. No gross abnormalities considering the age of the individual.
2. Minor deviations insufficient to cause any appreciable functional impairment.
3. Moderate deviations sufficient to cause appreciable functional impairment.
4. Severe deviations causing complete loss of hearing, vision, or speech.

E. *Excretory* function, i.e., bowel and bladder control.
1. Complete control.
2. Occasional stress incontinence or nocturia.
3. Periodic bowel and bladder incontinence or retention alternating with control.
4. Total incontinence, either bowel or bladder.

S. *Mental* and *Emotional Status*.
1. No deviations considering the age of the individual.
2. Minor deviations in mood, temperament and personality not impairing environmental adjustment.
3. Moderately severe variations requiring some supervision.
4. Severe variations requiring complete supervision.

PROFILE

P	U	L	S	E	S

The numerical values given to the various categories constitute the basis for the interpretation of the profile. This relieves the paramedical personnel, including social workers, of the difficult task of trying to interpret medical data. For instance:

> An 82-year-old man with mild diabetes not requiring strict dietary control or insulin, suffered a mild cerebrovascular accident on an arteriosclerotic basis, with a resultant right hemiparesis. He wears a brace and walks with difficulty. Aphasia is minimal. On occasion he is incontinent during the night and he has minimal cerebral changes.
>
> The profile would read as follows:
>
> P U L S E S
> 3 2 3 2 2 2
>
> He has five medical diagnoses which do not provide any indication as to his functional performance. Using the criteria of Table I, we would interpret the profile as follows: this is an individual who is ambulating with some difficulty. He requires some medical supervision. He has fairly good use of his upper extremities; wets the bed occasionally and has minimal signs of mental deterioration not requiring close supervision and control. From the environmental point of view, we infer that he would need placement in an institution with accessible physical facilities, including bathroom and living quarters located on one floor, where he could also obtain his meals.

It should be stressed that the profile is not intended to supersede careful medical diagnostic evaluation.

We have applied this type of profile screening to 115 patients, after a complete survey of their hospital and social records. The age distribution of these residents of the Westchester County Home is recorded in Table II. The large number of older persons reflects the character of the institution.

TABLE II. AGE DISTRIBUTION

AGE GROUP	NO. OF RESIDENTS
45–49	2
50–54	4
55–59	14
60–64	14
65–69	12
70–74	15
75–79	19
80–84	22
85–89	8
90–94	5
Over 100	
Total	115

Table III presents the various diagnoses encountered in the group. In most instances, there were multiple diagnoses for each individual. Diseases

of the vascular system, cerebral, cardiac or peripheral, were by far the most common. This substantiates the findings of other authors, including Goodman,[7] Connor,[8] and Hammond.[9] As explained in Table I, the cardiac status is included under the letter P. Thirty-two patients had arteriosclerotic heart disease and 26 were classified as having hypertensive cardiovascular disease. Only one patient was incapacitated to the extent that he could not function independently because of his cardiac status.

TABLE III. DIAGNOSTIC CATEGORIES

MEDICAL AND NEUROLOGIC		SURGICAL AND ORTHOPEDIC	
Cerebrovascular accident (8 aphasia)	34	Osteoarthritis	19
Arteriosclerotic heart disease	32	Fracture of neck of femur	14
Generalized arteriosclerosis	28	Other fractures	18
Hypertensive cardiovascular disease	26	Inguinal hernia	13
Peripheral vascular disease	25	Skeletal deformitories	10
Parkinsonism	13	Other surgical conditions	24
Alcoholism	13		
Cerebral arteriosclerosis	13		
Intrinsic cord disease	11		
Chronic emphysema	10		
Cataract	10		
Peptic ulcer	6		
Peripheral neuropathy	5		
Rheumatic heart disease	4		
Others	47		

The profile grades given the 115 residents are listed in Table IV. They reflect the physical character of the people who were screened. The preponderance of functional disability in the legs (L), as compared with the arms (U), could not be determined from the medical classifications of Table III.

TABLE IV. SUMMARY OF PROFILE CATEGORIES

	P	U	L	S	E	S
1	4	41	6	15	85	28
2	32	52	40	61	23	53
3	77	22	50	38	2	32
4	2	0	19	1	5	2

The lower extremity disabilities consisted essentially of static disturbances due to prolonged immobilization either in a wheelchair or in bed. The relatively few individuals with appreciable excretory dysfunction (E) reflected the selectivity of the study since most of the incontinent patients were not referred for the rehabilitation survey. About 33 per cent of the patients showed evidence of fairly advanced mental deterioration but were able to adjust to the Home environment. In several instances they had originally been certified for institutional psychiatric care.

It is apparent that fluctuations in the profile are possible without any change in diagnostic classification. Frequently a minor intercurrent infection or injury was sufficient to immobilize a patient and cause a downgrading in the physical profile. By suitable activation and rehabilitation, he could be restored to his previous functional level.

The physical profile can be used to depict an anticipated rehabilitation goal, with the existing profile as a base line. Periodic re-evaluation serves to rate either improvement in function, or conversely, further physical or mental deterioration.

SUMMARY AND CONCLUSIONS

1. Medical diagnoses do not accurately reflect the physical capacity of the chronically ill or aged person.

2. Disability evaluation, properly geared to this selected group, is necessary to supplement the medical diagnoses.

3. A method of disability evaluation adapted from the Physical Profile system utilized by the Canadian and United States Armies is proposed to fulfill this need.

4. Further field studies are indicated to confirm the applicability of this scheme under more varied conditions.

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Reviews

THE NATURAL HISTORY OF ULCERATIVE COLITIS

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INTRODUCTION

THE term ulcerative colitis was introduced in 1875 by Wilks and Moxon,[188] who wrote, "the term colitis is sometimes used as synonymous with dysentery. Our usual language has indeed been too indefinite, nay, incorrect, in speaking of all affections of the large intestine as dysenteric; for the true dysenteric process, although in many features like the simple ulcerative colitis, yet is a disease having certain definite characters." White[187] in 1895 noted that "the treatment unfortunately appears to have very little effect on the disease. Absolute rest in bed with slopped diet and opium, and hot fomentations if the pain and diarrhea are very severe, probably afford the best chance, but the prognosis is exceedingly grave."

There were early attempts to delineate the course of ulcerative colitis. Allchin[17] was able to gather 177 case reports of ulcerative colitis from three London hospitals for the period 1883 to 1908 and found that 55 per cent had died. The following year, Hawkins[77] reported on 85 patients, 41 of whom died. Of the 44 survivors, "many improved but I doubt if more than eight were cured. These figures being drawn from hospital and consulting work, naturally only include the severe and chronic cases. In all of the fatal cases, the colon was examined after death, and in all of these except one, the colon was extensively ulcerated, such ulceration not being due to typhoid fever, tuberculosis or other recognized cause. Until specific treatment can be provided, I do not think any dogmatic rules of treatment can be produced. I have nothing useful to say; but, looking back on the cases for which I have been responsible, I feel sure that lives might have been saved by an earlier recourse to colostomy."

The fact that ulcerative colitis continues to be a serious illness is evident from the more recent reports. Rice-Oxley and Truelove[149] in 1950 reported a

mortality rate of 22 per cent during the first year of the disease, and a 33 per cent mortality at the end of five years. Demole[40] noted that 40 per cent of patients coming to the hospital in their first attack died in the first year regardless of what type of treatment they received.

Ulcerative colitis also ranks as an important chronic disease, because of its protracted clinical course. Lockhart-Mummery[118] noted that cases of chronic colitis divided themselves into two classes: Those who would quickly get well and those who did not improve in spite of prolonged and careful treatment. "I think everyone who has had any experience in the treatment of chronic colitis will admit that this second type of case not only exists but forms an unpleasantly large proportion of the whole. The worst cases in the second class spent their time going from one doctor to another, and in visiting most of the English and continental spas. Many of them go in for Christian Science, vegetarianism, or other forms of quackery. In fact, they form one of the worst classes of chronic invalids, a nuisance to their doctors, their relatives, and themselves."

Attempts to delineate the natural history of idiopathic ulcerative colitis are fraught with many problems.[13,19,20,25,34,55,77,104,120,149,150,191] Agreement is lacking as to what should be classified as ulcerative colitis, both as to site of anatomic involvement and as to the presumed etiologic factors. Ulcerative colitis is not common and no single observer can accumulate a large series of cases. Further, an element of selection is present in all of the reported series of cases. Some clinics and hospitals, because of their special interest in the disorder, have attracted a larger following of patients who may not be representative of those seen in private practice or university clinics.

The clinical course of ulcerative colitis may be extremely variable. Not infrequently it is difficult to determine the time of onset of the disease. There may be little correlation between the clinical manifestations and the extent of the pathologic changes. Complications are not infrequent. In some patients the pathologic changes are limited to the bowel, while in others systemic complications may be an important part of the clinical picture.

Ulcerative colitis is one of the most difficult diseases to treat. It frequently runs a protracted and unpredictable course punctuated by numerous hospitalizations. A long follow-up is essential to establish a base line of the natural history of ulcerative colitis in order to evaluate new medical and surgical measures which have been introduced.[187] It seemed timely, therefore, to review what is known of the natural history of the disease. This review will concern itself with the definition and classification of ulcerative colitis, etiologic factors concerned in its development, pathologic changes observed, clinical features and course, local and systemic complications, and a brief consideration of the effect of therapy upon its natural history.

DEFINITION AND CLASSIFICATION

Ulcerative colitis has been defined as any regional, segmental, or general involvement of the large intestine including the rectum, which results in a bloody, bloody-mucoid, or bloody mucopurulent rectal discharge with or without fre-

quency in defecation.[141] The disorder presents itself in many forms, and therefore the term "chronic ulcerative colitis" is used to designate a group of serious maladies which may have varying etiologies. The diagnosis of chronic idiopathic ulcerative colitis is based upon history and physical findings and by correlation of these with sigmoidoscopic and roentgenologic alterations.[11,31] Ulcerative colitis is also known as idiopathic, nonspecific, and indeterminant, as colitis ulcerosa, colitis gravis, and as primary, suppurative, and thromboulcerative colitis.

Several classifications have been proposed, based upon either the etiologic concepts, the anatomic location of the disease, or the pathologic features. Bargen[8,9,11] has classified ulcerative colitis into nine types. The commonest form encountered in the North Temperate zone is the thromboulcerative colitis which is thought to be due to a streptococcus. Other types include tuberculous, amoebic, ulcerative due to lymphogranuloma venereum, ulcerative occurring as a late phase of bacillary dysentery, allergic, and colitis associated with nutritional deficiency syndrome. Bargen places "regional" colitis in a separate category and also differentiates "ulcerative colitis of unknown origin" from thromboulcerative colitis.

The anatomic extent of the colitis has been used as a basis for classification. The descending and sigmoid colon is the area of maximal pathologic involvement in ulcerative colitis. Involvement limited to this area has been termed *left-sided colitis*.[20,60,118] Occasionally the inflammatory changes may be limited to the sigmoid and rectal area. This appears to be a limited form of ulcerative colitis carrying a more favorable prognosis. Some have differentiated this from true ulcerative colitis.[21,55] Involvement of the entire colon is termed *universal colitis*.

Involvement of the ileum in ulcerative colitis is not infrequent but has been considered by most observers as a backwash phenomenon not representing primary ileal disease.[124] In 1936, Crohn and Rosenak[32] described 9 cases of combined ileitis and colitis. They regarded the process as an involvement of both the small and large intestine, usually synchronously. Various synonyms have been proposed for this disorder including *ileocolitis*, *right-sided colitis*, *enterocolitis*, and *segmental colitis*.[24,28,118,172]

Some feel that the whole picture of enterocolitis is that of primary ileitis which affects the small bowel primarily and spreads to the colon.[24,28,32] Butler[24] differentiates right-sided colitis into (1) that without ileal involvement; (2) that with varying degrees of ileal involvement; (3) segmental colitis; and (4) diffuse ileocolitis. He differentiates these conditions from ulcerative colitis. Felsen,[52] however, considers both regional enteritis and ulcerative colitis manifestations of the same disease. It is apparent that ulcerative colitis can extend into the ileum. There is also a tendency for right-sided colitis to extend along the bowel and present a picture indistinguishable from universal colitis.[21]

The clinical classification provided by Bargen, namely thromboulcerative colitis, regional colitis, and atypical or idiopathic ulcerative colitis, do not lend themselves well to pathologic correlation. Warren and Sommers[180] observed two processes which led to ulceration. Type A colitis was characterized by vasculitis, and type B colitis by crypt abscesses.

ETIOLOGIC CONSIDERATIONS

Chronic ulcerative colitis resembles peptic ulcer in that it appears to be the result of interaction of several etiologic factors.[6] The more important of these concern the roles of infection, allergy, the digestive enzymes and lysozyme, the parasympathetic nervous system, vascular factors, and the psyche.[62]

Infectious Factors.—The clinical features of idiopathic ulcerative colitis suggest an infectious etiology. A variety of organisms have been implicated as having a specific relationship to the development of ulcerative colitis including *B. proteus*, *B. pyocyaneous*, *B. lactus aerogenes*, *B. necrophorum*, beta hemolytic colon bacillus, gram-positive diplococci, the dysentery organisms, viruses, and *E. histolytica*. The two that have commanded most attention are the dysentery organisms and the gram-positive diplococci.

Hurst[81] suggested that ulcerative colitis was a chronic form of bacillary dysentery. Felsen[50] noted that *B. dysenteriae* was isolated from 2 to 60 per cent of cases of ulcerative colitis and reported an 8.2 per cent incidence of ulcerative colitis in patients with proved bacillary dysentery.[51] The more frequent occurrence of ulcerative colitis in family groups has also been used as support for an infectious etiology secondary to bacillary dysentery.[52] Although a small percentage of patients with dysentery develop a picture indistinguishable from ulcerative colitis,[54] there does not appear to be an important etiologic relationship.[23,75,78,161]

Gram-positive diplococci have been held responsible for the development of thromboulcerative colitis.[7] Bargen and Logan[15] were able to culture diplococci from the ulcers in 80 per cent of patients with ulcerative colitis. Acute ulcerative colitis developed in experimental animals following injection of these organisms. Hemorrhagic infiltrations and ulcers also developed in 50 per cent of animals following injection of diplostreptococci isolated from an abscessed tooth of a patient with active colitis. Injections of cultures from patients without colitis did not result in experimental colitis. Despite these interesting observations, most investigators believe that the diplococcus is not the primary etiologic agent of ulcerative colitis but rather that it is a secondary invader.[78,80,142,147]

Bacterium necrophorum was found by Dack, Dragstedt, and Heinz[35] to be the predominant organism in the isolated colon of three patients with ulcerative colitis. The organism persisted as a predominant type as long as the colon remained severely diseased but was less frequent during periods of remission. Complement-fixing antibodies for *B. necrophorum* were reported. Although this organism can be found in as many as 70 per cent of patients with chronic ulcerative colitis, ulcers could not be produced by administration of the organism by mouth, by rectal instillation, or by introducing the organism into the isolated colon of experimental animals.[41]

The similarity of the stenosing rectal lesions of lymphogranuloma venereum to those of ulcerative colitis suggest that there might be some relation between the two diseases. However the Frei test is negative in the majority of patients with ulcerative colitis

A viral etiology has been suggested for ulcerative colitis.[134] A filtrate of intestinal mucosa injected intravenously resulted in lesions of the bowel which

were concluded to be the result of a filtrable virus. No primary isolation studies of viruses have been reported in this condition.

Chronic colitis indistinguishable from idiopathic ulcerative colitis occasionally is seen in patients with previously documented history of amoebic colitis. This may occur years after the initial episode of amoebic colitis.[54]

A process picture resembling the acute phase of ulcerative colitis has been produced by administration of Shiga toxin,[141] by prolonged administration of Mecholyl,[129,183] and by sensitization with egg albumin.[101] Occasionally amoebic colitis results in a picture which resembles idiopathic ulcerative colitis. Bacillary dysentery may resemble ulcerative colitis. However, even when these conditions are eliminated, the majority of cases remain without a specific known cause.[181]

Allergic Factors.—Andresen[2] reported that 66 per cent of patients responded to dietary management in such a manner as to suggest that food allergy was responsible for the disease. Mucous membrane hypersensitivity could be produced in animals and humans following local injection into the bowel of human serum containing reagin antibodies for peanut oil.[69,70,179] Subsequent administration of peanut oil by mouth produced edema and hyperemia at the site of the previous injection. The colon appears to react similarly to sensitization with egg albumin.[101]

The possibility of sensitization of the colonic mucosa to the products of digestion has been considered. Victor and co-workers[178] administered bacteria-free filtrates from patients with ulcerative colitis to monkeys without effect. If the bacteria-free filtrates were incubated with sections of skin or bowel, these filtrates were found to have a disintegrating effect upon human epithelium.[164] The source of the factor responsible for this has not been identified.

Role of Enzymes.—Increased concentrations of lysozyme are found in the stools of patients with ulcerative colitis.[65,148] Lysozyme is capable of removing the protective mucus of the colon, thus favoring ulceration of the denuded mucosa by the bacterial flora.[127] Some investigators have reported the development of ulcerative lesions following administration of lysozyme[128] while others found no effect.[130,136] The high lysozyme titer in the stool of patients with ulcerative colitis appears to be due to the high concentration of the enzyme in granulation tissue and leukocytes.[79,154] The results of treatment with antilysozyme agents are not impressive,[114] and lysozyme appears merely to reflect the activity of the ulcerative process.

Damage to the colonic mucosa may follow instillation of trypsin into the colon of dogs.[144] However, the colonic mucosa is not injured by trypsin following transplantation of such mucosa to the duodenum just beyond the ampulla of Vater. Pancreatic function is not increased in ulcerative colitis[42,110] and may actually be decreased.[42]

Vascular Factors and the Parasympathetic Nervous System.—Hyperactivity of the parasympathetic nervous system may be related to the development of ulcerative colitis.[131] Transient edema, submucosal hemorrhages, and erosions can be produced following Mecholyl administration.[137] Prolonged administration, however, will result in vascular hyperemia, increased capillary permeability and superficial necrosis,[137] which is followed by bloody diarrhea.[183]

Ulceration tends to overlie the taenia, and it has been suggested that sustained contraction of the longitudinal muscle fibers might predispose to ulceration.[113] A threefold increase in the number of ganglion cells has been noted in patients with chronic ulcerative colitis as compared to normal subjects.[163] It is not clear whether the increase in ganglion cells are primary changes or whether they are the result of long, continued hyperfunction.

The importance of vascular factors has been emphasized.[39,180] What role hypersensitivity states or alterations in the parasympathetic nervous system play in the vascular alterations is not known.

State of the Intestinal Wall.—A deficiency in the intestinal wall rendering it more susceptible to ulceration has been suggested as being important,[61] and improvement has been reported following administration of intestinal extracts.[58,61,76,165]

The similarity of the clinical manifestations of ulcerative colitis to those observed in patients with collagen disease has suggested that ulcerative colitis may be related to this group of disorders.[111] The pathologic changes sometimes resemble those seen in periarteritis nodosa.[180] Degeneration of the basement membrane of the mucosa has been demonstrated in biopsy studies.[111] This may be a relatively specific phenomenon for ulcerative colitis and unrelated to leukocytic infiltration,[87] or a nonspecific sequela secondary to inflammation and leukocytic infiltration.[159]

Role of the Psyche.—The role of the psyche in the development of ulcerative colitis has received increasing attention.[33,36-38,44-47,64,67,68,71-73,94,95,112,122,135,138,143,145,146,158,160,162,166,170,190,191] A high proportion of patients with ulcerative colitis are described as manifesting obsessive-compulsive character traits including neatness, orderliness, punctuality, conscientiousness, obstinacy, and immaturity.[46] Oversensitivity, egocentricity, fearfulness, excessive need for love, sympathy and affection, passivity, repressed hostility, indecision and dependency are all prominent features of such patients.[122] The relationships of ulcerative colitis patients with people in general are restricted. They may have a very dependent relationship with one or two persons but usually lack the capacity to establish warm friendships with others. Frequently one person assumes the key role in the psychosocial activities of the patient. This key figure, usually the mother or mother-substitute, is depended upon for guidance, advice, and direction.

The mothers of patients with ulcerative colitis are described as domineering, cold, unaffectionate, punitive, rigid, strict, and judgmental.[46] The mothers may have an ambivalent relationship to the child in that they attempt to maintain the child in life-long dependence to satisfy their own needs, and in addition, show unconscious destructive impulses toward the child.[160]

Ulcerative colitis frequently appears when the patient faces a life situation which requires some outstanding accomplishment for which he is unprepared. There is usually a close temporal relationship between the stressful circumstances and the onset of the disorder. Real, symbolic or threatened separations from the key figure are frequently involved.[46]

Ulcerative colitis patients with bowel fistulas have been utilized in an attempt to correlate life-stress situations with the behavior of the bowel. Situ-

ations provocative of fear, pain, or anxiety were associated with hypofunction of the bowel.[66,184] Life situations provocative of conflict which were associated with feelings of anger, resentment, and hostility were associated with hyperfunction.[123,184]

Although psychic factors appear to be important in the development of ulcerative colitis, many questions remain unanswered. The personality changes mentioned are not specific for ulcerative colitis but occur in other disorders and in patients without disease. We know little about the personalities of patients prior to the development of ulcerative colitis.[94,160] Marked anxiety and rage were reported prior to the onset of colitis in a psychoanalytic study of two patients.[94] The attacks generally began within a few weeks after a sudden unforeseen threat to the security of the patient's self-esteem. The colitis itself was associated with distorted self-destructive tendencies.

Engel[46] has attempted to formulate the psychologic observations into an acceptable scheme. Ulcerative colitis develops in particular individuals under specific circumstances. Colitis involves particularly the lining surface of the bowel. The lumen of the bowel, even though its lining surface is of endodermal origin, is part of the boundary between the body and the external environment. The tissue reactions in the colon develop only when other adaptive processes fail and a significant relationship with the key figure is threatened or interrupted. Biologic and psychologic developmental factors may determine the bowel as the site of tissue breakdown. The traumatic process may be accompanied by biochemical or physiologic derangements which permit the development of ulcerative colitis.[48]

The pathogenesis of the tissue response in ulcerative colitis is not clear. No pathognomonic causative organism has been identified, although it appears that bacteria have an important role in the maintenance of the ulcerative process. Hyperfunction of the bowel,[39,80,133] hypersensitivity states, or alterations in the vascular response could predispose to ulceration.[101] As Zetzel[191] points out, "Experimental evidence calls attention to alterations in the vasomotor state of blood vessels as the mechanism for mucosal lesions and ulceration. However, for the present, it leaves too many open links in the chain connecting emotional conflicts, imbalance of the autonomic innervation of the large bowel and ulcerative colitis as seen clinically."

PATHOLOGIC ALTERATIONS

Proctoscopically four processes can be distinguished: (1) diffuse hyperemia, (2) edema, (3) multiple superficial abscesses, and (4) coalescence of abscesses with the formation of larger ulcers. The ulcers may vary in size from punctate lesions to linear ulcers extending throughout the entire length of the large bowel. The mucosa between the ulcerations is erythematous, edematous, and may be entirely denuded. Perforation through the entire intestinal wall may occur occasionally. Increasing fibrosis, secondary to ulceration and attempts at healing, results in thickening of the bowel wall, shortening of the colon, and occasionally localized stricture formation.

The transverse, descending, and sigmoid colons are involved in 80 per cent of cases.[181] The cecum and ascending colon are diseased in about 65 per cent

of cases. Colitis restricted to the right side is noted in only 2 per cent of cases.[180] Ulceration involves the distal ileum in about one-third of cases.[124,181]

The inflammatory changes involve primarily the mucosa and submucosa. The continuity of the epithelium is interrupted by ulcers whose base consists of an infiltrate of lymphocytes, plasma cells, eosinophils, and macrophages. There is little granulation tissue or proliferative change.[172,181]

Two processes appear to be important in the development of ulcerative colitis, vasculitis, and crypt abscesses. Vasculitis was found in 11 per cent of the 180 cases reported by Warren and Sommers.[180] These cases were characterized by more extensive and deeper ulcerations. The lesions in the blood vessels were often identical, except for location, to those of periarteritis nodosa or thromboangiitis obliterans. Interference with the local vascular supply would lead to denuding of the mucosa and damage of the wall beneath it, with the ultimate development of gangrene and perforation.

Crypt abscesses were more common, occurring in 39 per cent of the patients. They were characterized by the appearance of polymorphonuclear leukocytes within the lumen of the mucosal crypts. The leukocytes formed a crypt abscess which would rupture, spilling its contents into the submucosa. Dissection occurred beneath the adjacent epithelium which then ulcerated away. In more than half of their cases, Warren and Sommers could not indicate how the colitis had developed.

CLINICAL FEATURES

Incidence.—Idiopathic ulcerative colitis, although a relatively rare disease, is world-wide in its distribution. There are important differences, however, in its frequency in various areas. It is less prevalent in the warmer climates of the United States and is infrequent in the Central American countries.[177]

Kantor[93] reported nine cases of ulcerative colitis among 2,500 private patients seen for digestive troubles in the United States. Spriggs[161] reported five cases per thousand hospital admissions in England. Melrose[125] reported a higher incidence and noted that the disease was more common in England than in Scotland. The frequency of ulcerative colitis in Denmark and Finland was similar to that noted in Scotland.[126] The frequency in Belgium is approximately the same as that in England while the disorder is least frequent in Switzerland.[40,126] There are no sex differences in its distribution.

Age at Onset.—Ulcerative colitis is most common in the second and third decades.[141,189] It is less common in later life, although a sizable group of cases have been reported whose onset began in the fifth, sixth, and seventh decades.[5,49,161,171,189]

Ulcerative colitis has been reported in newborn infants[18] and is not uncommon in children.[43,109,176] Kirsner and co-workers[105] observed 80 instances of ulcerative colitis in children during an eighteen-year period, and Bargen and Kennedy[14] reported on 139 cases in children during a ten-year period.

Symptomatology.—The passage of blood and mucus, diarrhea, abdominal cramps, and tenesmus are the most important symptoms of ulcerative colitis. The onset may be insidious. More frequently the onset is abrupt, being ushered

in by melena and diarrhea. In the acute fulminating type, the patient may have almost continuous evacuations composed of blood, pus and mucus. Abdominal pain is common. Characteristically it has a relationship to the time of defecation. Fever, weakness, tachycardia, malnutrition, and mental abnormalities may be observed.

Clinical Course.—The clinical course of nonspecific ulcerative colitis is extremely variable. The disease may have a sudden or insidious onset, and may pursue a fulminating or slowly progressive course with exacerbations and remissions for many years.[20,77,78,80,104,155]

A number of classifications have been suggested to characterize the clinical course of ulcerative colitis. Monaghan[132] divided his cases into an acute group, which were subdivided into mild, fulminating, and continuous; and a chronic form which included both the continuous and relapsing type of disease. Maratka lists three types: remittent, intermittent, and mixed.[11] Bone and co-workers[20,171] used the classification based on the severity of the patient's illness when first seen. The classification was dependent upon clinical data, including the amount of diarrhea, the amount of blood in the stools, fever, weight loss, anemia and constitutional symptoms. The patients with mild disease had less than five stools a day and few systemic manifestations. Patients classified as moderately severe usually had five to ten stools per day with blood, low-grade fever, 10 to 15 pound weight loss, slight secondary anemia and partial disability. Patients with more advanced disease were classified as severe. This classification is almost identical to that employed by Flood and co-workers.[55] An additional classification of fulminating ulcerative colitis has been used to refer to those patients whose clinical course has been rapid from the beginning.[155,171]

The clinical course of patients during the follow-up period may be divided into four groups: (1) those patients who had recovery between attacks, (2) those who had improvement between attacks, (3) those with continuous symptoms and (4) those who had a fulminating course.[20]

It is difficult to arrive at a true estimate of the mortality rate of ulcerative colitis. The samples dealing with mortality rates frequently differ markedly. The severity of the disease under study also differs. Thirty-five years ago, the

TABLE I. MORTALITY RATE IN ULCERATIVE COLITIS

AUTHOR	DATE	NUMBER OF PATIENTS	PER CENT MORTALITY
Allchin[1a]	1908	177	55
Hawkins[77]	1909	85	48
Hern[78]	1931	50	40
Hardy and Bulmer[75]	1933	95	33
Kiefer[97]	1936	55	18
Crohn and Rosenak[30]	1936	75	10
Buzzard et al.[25]	1938	—	28.5
Willard et al.[189]	1938	71	29
Hopping and Bargen[83]	1942	329	8
Kirsner et al.[104]	1948	100	14
Bone et al.[20]	1950	112	17
Rice-Oxley and Truelove[149]	1950	121	22–33
Wheelock and Warren[185]	1955	343	44
Demole[40]	1956	—	26

mortality rate was observed to be 50 per cent.[77] The mortality rate in a collected series of more than 1,200 cases up to 1949 was 17.3 per cent.[180] There are two reports since 1950 which report mortality rates above 30 per cent.[40,149] The mortality rates in some of the reported series are indicated in Table I.

The mortality rate does not give the complete picture of the devastating nature of the disease. Long-term follow-up studies are essential.[186] Wheelock and Warren[185] reported on 713 patients treated for ulcerative colitis between 1915 and 1949. Of those who could be traced who had been followed for ten years or longer, 155 (45.3 per cent) were living, and 188 (54.7 per cent) were dead. Ulcerative colitis was directly responsible for 81 per cent of the deaths. The major causes of death were peritonitis, hemorrhage, toxicity, carcinoma of the colon, or pneumonia. Forty-six of the 153 patients who died as a result of ulcerative colitis had been treated medically while the remaining 107 had received surgical treatment.

Bargen and co-workers[16] reported a survival rate of patients of 57.8 per cent twenty-five years after the diagnosis of ulcerative colitis had been made. A comparison of their survival data for chronic ulcerative colitis as compared with a hypothetical normal population is shown in Fig. 1.

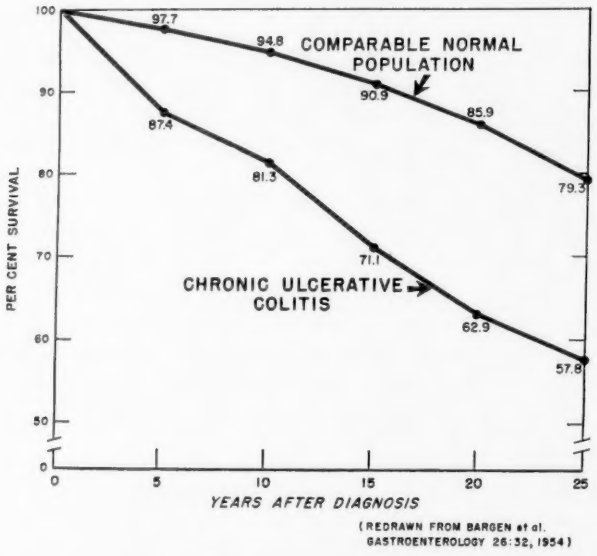

Fig. 1.—Survival curve for patients with ulcerative colitis.

The disability from ulcerative colitis is weil out of proportion to its incidence. Kirsner and Palmer[102] report "that among 120 patients, the duration of symptoms exceeded five years in 67 cases; in 31 the disease had continued for 10 to 20 or more years. Multiple admissions to the hospital had been necessary in 105 patients of the series; 23 had required 6 to 15 hospitalizations. The total number of hospital days for each patient exceeded 100 in 48 cases and 200 in 19 cases and ranged from 471 to 718 days in four cases."

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FACTORS RELATED TO PROGNOSIS

The most characteristic feature of ulcerative colitis is the unpredictability of its clinical course. "Frequently it is impossible to determine when the patient is first seen what is likely to happen in ensuing months and years."[20] In some patients, the illness is relatively mild, being limited to the rectum and rectosigmoid, and on roentgen examination, the bowel appears normal. In others, whose symptoms are severe, proctoscopic changes are pronounced and varying involvement of the colon is demonstrable by x-ray. A small group of patients have minimal symptoms in spite of extensive evidence of disease. In general, the tendency is for ulcerative colitis to progress, although a few cases have been reported to have demonstrated clinical reversibility including complete disappearance of x-ray evidence.[103] Some factors are of value in predicting the subsequent clinical course and prognosis of ulcerative colitis.

Age at Onset.—The disease is more severe in patients who are very young at the onset of the disease.[14,20,85,104,105] Six of nine medical deaths in Kirsner's series[105] occurred in patients under 25 years of age, while four of these occurred in patients under the age of 20. Not only is the disease more severe in children, but there is an increased incidence of complications.

Ulcerative colitis having its onset in later years also appears to be more serious than that seen during the middle years.[5,20]

Initial Severity of the Disease.—The prognosis of the patient with ulcerative colitis is related to the initial severity of the disease. Eighty per cent of patients who were classified as mild initially, improved or recovered, whereas 70 per cent of those classified as severe became worse or died.[20] Fifty per cent of this latter group required surgical treatment.

Duration of Disease.—Most observers report that ulcerative colitis is more severe during its first year or two.[40,104,149,180] Thirty-seven per cent of 60 fatal cases, reviewed by Warren and Sommers,[180] had been ill for less than one year. A 22 per cent mortality within the year of the first attack was reported by Rice-Oxley and Truelove,[149] while Demole[40] reported a 40 per cent mortality rate during the first attack regardless of the type of treatment administered.

Flood and associates[55] could find no correlation between the duration of the disease and the prognosis.

Rate of Response to Treatment.—The early symptomatic response to treatment usually has little prognostic significance.[55,120] The rate of response to treatment is of more value in relationship to the subsequent course of the illness. The acutely ill patient who fails to respond during several weeks of intensive medical treatment may require early surgery. The antibiotics and sulfonamide group of drugs appear to be of little value in this group of patients but the response to induced hyperadrenalism may be rather dramatic.[55,171] The prognosis for this group of patients prior to the use of adrenal cortical steroid therapy was very serious.[20] Even with the use of adrenal steroid therapy, the incidence of recurrences in patients with fulminating disease remains high.[171]

Those patients with less severe but continuous symptoms also have an unsatisfactory long-term course.[55,78] More than half of the patients in the

series of Bone and co-workers,[20] who improved but did not recover between attacks, either became worse or ultimately died of their disease.

Extent of Anatomic Involvement.—Patients whose colitis is characterized microscopically by vasculitis have a higher mortality and a poorer prognosis than those whose pathologic picture is that of crypt abscesses.[180] There is also a rough correlation between the anatomic extent of the disease and subsequent clinical course. Left-sided involvement of the colon carries a more favorable prognosis than either universal or segmental colitis.[13,20,60] The relatively benign course of colitis limited to the rectum and sigmoid has prompted some to segregate this entity from either universal or right-sided colitis.[21,55] Patients with left-sided colitis may have retrograde extension of their disease and may develop all the complications associated with generalized colitis.[11,97,104]

The course of patients with universal colitis is variable. They may frequently get along very well on a conservative management for long periods of time.[104] Usually, however, they have more manifestations of their disease than patients who have only partial colonic involvement.[13,20,55,60]

Segmental colitis or right-sided colitis follows a rapid course and carries a poor prognosis.[13,21,24,60,104] Those with diffuse ileocolitis have the poorest prognosis.[24,126]

Significance of Proctoscopic Changes.—The proctoscopic appearance usually parallels the clinical course of the disorder,[20,55] although there are a few patients who show an inflamed mucosa with comparatively mild symptoms.[104] Flood[55] has observed that the proctoscopic remission may lag by months or years behind the subsidence of symptoms. Most patients who are clinically well between attacks were found to have a normal protoscopic picture.[20,55] Patients who had incomplete recovery between attacks or continuous symptoms showed little improvement in the proctoscopic picture.

Although there have been attempts to correlate the proctoscopic appearance with the duration of the disease,[31] there seems to be little correlation.[104,132]

Significance of Roentgenologic Changes.—The x-ray changes in ulcerative colitis vary from a normal appearance to definite x-ray evidence of ulceration in the form of fine serrations. Rigidity, shortening of the colon, and pseudopolyposis may develop with the passage of time. In most instances, the disease involves the colon either partially or completely during the initial episode and remains relatively stationary thereafter.[20,55,103,150] A smaller group of patients may show subsequent spread either in a clockwise or counterclockwise manner.

Ricketts[150] reported regression in the roentgen appearance in 10 per cent of patients, progression in 25 per cent, and no change in 65 per cent. Occasionally the roentgen manifestations may completely disappear.[103]

Other Factors Related to the Course of the Disease.—Emotional trauma frequently precedes the onset or a relapse of ulcerative colitis. Kirsner[104] reports the most common factors to be death or separation of parents, marital problems, and disruption of the home.

Occasionally ulcerative colitis has been noted to follow the use of laxatives, in particular castor oil.

Pregnancy appears to have little effect upon colitis which was inactive at the time of pregnancy. If pregnancy is superimposed on active colitis, the disease may be aggravated.[1,57,92,106,108,140,174] Colitis which has its beginnings early in pregnancy is particularly virulent and may end fatally.[191]

The appearance of systemic complications usually worsens the prognosis. Both erythema nodosum and pyoderma gangrenosum are poor prognostic signs.

COMPLICATIONS

The complications of chronic ulcerative colitis are numerous, varied, and often serious. They can be classified into local complications which arise from the bowel, and systemic complications.

Local Complications.—Local complications include perirectal and perianal infection, stricture formation, hemorrhage from the bowel, perforation of the colon with peritonitis, the development of polyposis, and carcinoma.

Polyps: The incidence of adenomatous polyps varies from about 10 to 19 per cent.[1,86,104,151,157] Polyps were found in 19 per cent of 2,000 cases studied by Sloan, Bargen, and Baggenstoss.[157] The polyps were multiple in 75 per cent of patients and diffuse polyposis was present in 9.3 per cent. The incidence of polyps was higher in cases with severe ulcerative colitis.

In addition, pseudopolyps develop secondary to the recurrent ulcerating and healing process. These have little clinical importance, merely indicating a more severe form of the disease, whereas adenomatous polyps may ultimately become malignant.

Stricture: The incidence of stricture of the bowel varies considerably.[20,104,151,157] Sloan[157] reported an 11 per cent incidence of localized narrowing of the rectum or colon to a lumen of 1.5 cm. or less in diameter. The commonest sites were the rectum and sigmoid. The incidence of stricture tended to be high if the patient had severe ulcerative colitis or if the onset of the disease occurred before the patient's forty-fifth year. Kirsner and associates[104] reported an incidence of 19 per cent. Others report that stricture is relatively rare.[21,51] Occasionally the stricture is so marked as to obstruct the lumen of the bowel producing intestinal obstruction.

Perirectal and perianal complications: Perirectal and perianal infection occurs in 4 to 17 per cent of patients.[20,104,151,157] The most common of the rectal complications is that of rectal fistula which not infrequently extends to form a rectovaginal fistula in women.[157]

Hemorrhage: Massive hemorrhage appears to be a commoner problem in reports from hospitals and large metropolitan areas,[104,151] than from reports from clinic groups.[157] Massive hemorrhage was responsible for or associated with fatal termination of the disease in 12 of 22 patients in one series.[157] The seriousness of bleeding may be aggravated by other factors affecting the clotting mechanisms such as hypoprothrombinemia.[104,151]

Perforation: The incidence of perforation in the series reported prior to the use of adrenal steroid therapy varied from 3 to 6 per cent.[20,104,151,157] Most

of the patients developing perforation went on to develop localized or generalized peritonitis. Formerly, most of these patients ran a fatal course, although the prognosis has improved with the introduction of antibiotics. The frequency of perforation treated with ACTH and cortisone appears to be higher than in patients not so treated.[169,171]

Carcinoma of the colon: Although pathologists in the past have denied a relationship between the incidence of ulcerative colitis and cancer of the colon, more recent studies have emphasized the effect of polyps upon the subsequent development of cancer in the ulcerated colon.[29,180] Carcinoma appears to result from two processes: first, neoplastic mucosal polyps are present in patients with ulcerative colitis to the same degree as in the general population and have the same tendency to become malignant, accelerated perhaps by chronic inflammation; second, degeneration of mucosal epithelium continues despite repeated ulceration, and a precancer epithelial hyperplasia may develop in an unfavorable environment.[180] Some of the cases of carcinoma secondary to colitis may represent cases of multiple polyposis which subsequently develop a picture of colitis, which then obscures the underlying polyposis. Inflammatory pseudopolyps, because of their structure, are least likely to undergo any neoplastic change.[29,180]

The incidence of carcinoma in relation to ulcerative colitis ranges widely in the reported literature.[17,26,29,53,59,63,98,117-120,156,168,180,182,191] An incidence of 1.3 per cent of carcinoma was found in 1,467 cases of ulcerative colitis reported to 1944.[117] Machella[120] reviewed the major reports from 1944 to 1951 and found the incidence of carcinoma to be 3 per cent of 6,890 cases with a range of 0 to 7 per cent. This probably does not represent the true incidence of carcinoma as this could be obtained only by examination of the colon in each patient by the pathologist. Furthermore such a figure would also have to be corrected for the natural incidence of carcinoma.[16]

The incidence of carcinoma obtained from surgical and autopsy specimens is higher than that based on roentgen and sigmoidoscopic study. The incidence of carcinoma diagnosed microscopically was 4.4 per cent in 226 patients, 214 of whom underwent total colectomy and 12 of whom came to autopsy. The incidence of carcinoma was only 1.9 per cent in the patients studied by x-ray and sigmoidoscopy.[98] Warren and Sommers[180] found a 5 per cent incidence of carcinoma of the colon at autopsy. Four additional patients were noted to have foci of precancerous epithelial hyperplasia. All had an average duration of their colitis of more than ten years.

Cancer has been found to be more frequent in younger persons with ulcerative colitis of more than ten years' duration,[98] and in those cases in which the onset of the disease occurred before the patients were 10 years of age.[157] The tendency for the incidence of carcinoma to rise with increasing duration of the disease is illustrated by Lyons and Garlock.[118] Carcinoma was found in 3.9 per cent of 226 surgically treated cases of ulcerative colitis. However, in the patients who had chronic ulcerative colitis for more than twelve years, 36 per cent developed carcinoma; and in 16 cases of chronic ulcerative colitis involving the rectum for over twelve years, 43 per cent developed carcinoma.[118]

Only 8 of 73 patients (11 per cent) with adenocarcinoma of the large intestine associated with ulcerative colitis had had ulcerative colitis for less than five years; and only 18 patients (24.7 per cent) had ulcerative colitis for less than ten years.[156] Eighty-eight carcinomas were found in the 73 patients, 44.3 per cent of these being of grade 3 or 4 malignancy. There were only two five-year survivors and 57 of the 73 patients died of carcinoma. The multicentricity of the tumors were striking in 40 specimens. The incidence of pseudopolyposis was higher in patients with multicentric carcinoma.

The incidence of carcinoma of the colon is at least four times more frequent in patients with colitis than it is in the general population of the same age groups.[118,119] Bargen and co-workers[16] found that cancer occurred, on the average, 30 times more frequently in the colitis group than it would have in a normal sample. The incidence of carcinoma diagnosed microscopically in Kiefer's series[98] was 66 times the expected incidence.

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The implications of these figures are pertinent to the management of the patient with ulcerative colitis. The frequency of malignant degeneration does not appear to be sufficiently hazardous to warrant the recommendation of total colectomy for this reason alone.[16,98] Data indicate that ileostomy alone has little role at the present time in the surgical management of the patient with ulcerative colitis, since it does not protect against the subsequent development of carcinoma.[26,63] The increased incidence of carcinoma arising in children who develop ulcerative colitis,[85] the increasing incidence with increasing duration of the disease,[16,26,63,118] as well as the virulence of the lesion and the poor prognosis once the disease is recognized,[26,98,156] can be marshalled in favor of a more aggressive surgical approach to the treatment of ulcerative colitis.[145] Also pertinent is the difficulty in diagnosing carcinoma in the patient with ulcerative colitis, even utilizing the methods of exfoliative cytology.[59] Furthermore, the fact that ulcerative colitis is quiescent for ten or more years gives no assurance against the development of a secondary adenocarcinoma.[156]

Systemic Complications.—The systemic complications of ulcerative colitis include those which result from the nutritional and metabolic disorders secondary to ulcerative colitis as well as complications affecting areas of the body other than the colon.

Nutritional deficiencies: Nutritional deficiencies can result from inadequate intake and utilization of food, absorptive difficulties, and losses from diarrhea.[121,175] Anemia and hypoproteinemia are frequent in patients with ulcerative colitis. Occasionally the albumin-globulin ratio may be reversed, chiefly because of reduction of the albumin fraction.[104] Deficiencies of potassium may occur secondary to the fecal losses,[116] or as the result of ileostomy.[3] Deficiencies of the fat soluble vitamins may be reported.[175] Steatorrhea frequently accompanies nonspecific enterocolitis.[28]

Liver disease: Alterations in the liver occur in ulcerative colitis.[10,82,90,91,99,107,139,152,153,173] The changes include fatty,[10,90,107] degenerative[99] and inflammatory changes,[10,99,107] cirrhosis,[10,82,90,99,107] and multiple liver abscesses.[177]

The relationship of the liver disease to colitis is not clear. Evidence of clinical dysfunction of the liver is not striking.[152] The most frequent morpho-

logic change is fatty infiltration of the liver, which may be noted at the time of autopsy,[90] or from the living patient by a study of needle biopsy.[10,107] Alterations in the liver appear to be more frequent in patients with, than in those without, ulcerative colitis.[99] These changes are both degenerative and inflammatory.

The relation of colitis to the development of cirrhosis is not clear. Some report that cirrhosis is rare.[90,99,139] Kleckner,[107] who reported cirrhosis more frequently, suggested that the absorption of large numbers of bacteria or their toxic products might be a likely cause. The frequency may be greater than generally realized. Figures based upon autopsy findings in patients dying with ulcerative colitis (especially if the disease has been of short duration) may not indicate the true incidence of cirrhosis.[82]

Arthritis: Arthritis is also observed in association with ulcerative colitis.[20,22,80,102,104,191] The incidence of arthritis ranges from about 4 to 8 per cent. The pattern of the arthritis varies from migratory joint pains to the clinical picture of rheumatoid arthritis.[55]

Skin complications: Skin complications are reported in 11 to 13 per cent of patients.[22,104] Samitz and Greenberg[153] who included buccal lesions, reported that 34 per cent of patients with ulcerative colitis had one or more skin complications. Aphthous ulcers occurred in about 30 per cent, while ulcerations elsewhere and pyoderms were present in 24 per cent.

Erythema nodosum, a complication usually associated with hypersensitivity states, was noted in 19 per cent of the cases reported by Foster and Brick.[56] Erythema nodosum was frequently associated with arthralgia and conjunctivitis. ACTH seem to induce a rapid remission in the skin lesions but these frequently recurred.

Pyoderma gangrenosum, consisting of single or multiple necrotic ulcers of the skin, is the most outstanding skin lesion associated with ulcerative colitis. The ulcers spread rapidly as the result of necrosis of the underlying subcutaneous tissue and denude large areas of the thoracic or abdominal wall. Pyoderma gangrenosum indicates a poor prognosis.

Miscellaneous conditions: Other conditions found in association with ulcerative colitis include clubbing of the fingers, arteritis, and vascular thromboses.[102] A few patients develop amyloid disease. Subclinical glomerulitis[88] and interstitial pancreatitis[4] may be observed at autopsy.

EFFECT OF THERAPY UPON THE NATURAL HISTORY OF ULCERATIVE COLITIS

The effect of therapy upon the natural history of ulcerative colitis is most difficult to evaluate.[120,169] The therapeutic agents which have been employed include sulfonamides, antibiotics, preparations of hog stomach and intestine, antilysozyme agents, cortisone and related adrenal steroids, corticotropin, and psychotherapy. Good results were reported in 57 per cent of patients treated with sulfonamides, 61.6 per cent treated with antibiotics, 65.9 per cent treated with antilysozyme agents, 44 per cent treated with cortisone, and 67 per cent treated with ACTH.[120] The results with preparations of hog stomach and intestine varied widely.[120] Comparable results have also been reported with

the use of psychotherapy.[64,68,71-73] Satisfactory symptomatic results can be expected from the first three months of treatment in about 65 per cent of patients, but only one out of two follow-up years may be regarded as satisfactory regardless of the type of therapy.[55]

Corticotropin and some of the adrenal steroid hormones are capable of suppressing abruptly and dramatically the clinical manifestations of the acute inflammatory phase. Their use in the fulminating and seriously ill patient has the effect of reducing the mortality rate of these patients, many of whom will eventually require surgery. Jones[89] reports clinical remissions in 40 per cent of patients receiving cortisone therapy at the end of six weeks of treatment as compared with 17 per cent of patients receiving placebo therapy. Adverse effects from these preparations have been described[12,171] and further observation will be necessary to determine whether the use of induced hyperadrenalism will modify the long-term course of the disease.

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Although marked remissions may occur on medical and supportive treatment, a curative agent capable of reversing the pathologic alterations of the disease is not available. Even patients who enter into a stage of clinical remission usually retain some stigmata indicative of previous inflammatory disease, and a sustained clinical remission cannot be interpreted as an assurance that the patient may not subsequently develop carcinoma.

The disability from ulcerative colitis in terms of chronic invalidism, loss of time from work, inability to hold gainful employment, curtailment of normal social activities, and impoverishment by long periods of hospital care is great in spite of good medical management. Some surgeons now feel that employment of modern surgical techniques provides a better means for preventing deaths and minimizing or abolishing the complications which lead to disability. Bates[17] states, "In fact, the only cure for the disease now possible is colectomy. Payment is exacted in terms of an operative mortality, surgical complications early and late, loss of the colon, and permanent ileostomy. Is the price too great?" Many, both patients and physicians, feel that it is.

SUMMARY

Chronic ulcerative colitis is used to designate a group of serious maladies which may have varying etiologies. However, when the known etiologic factors are excluded, the majority of cases remain without a specific known cause. It is probable that the entity, idiopathic ulcerative colitis, is the result of the interaction of several etiologic factors including infection, allergy, vascular alterations, and an imbalance between the autonomic nervous systems. The important temporal relation between psychic trauma and the development of ulcerative colitis has been emphasized.

Gross pathologic changes include hyperemia of the mucosa, edema, superficial abscesses, and coalescence of abscesses with the formation of larger ulcers. These processes appear to be the result of two processes: vasculitis with ischemia of the mucosa and submucosa, and the development of crypt abscesses which rupture into the submucosa.

The most characteristic feature of the clinical course of ulcerative colitis is its variability. The onset may be sudden or insidious. It may pursue an intermittent or continuous course for a period varying from a few weeks to many years. Certain factors are of value in predicting the subsequent clinical course. Factors suggesting a poor subsequent prognosis are: onset in either the very young or very old, a severe initial attack which carries a higher mortality rate, lack of response to treatment, segmental or right-sided involvement of the bowel, lack of improvement in the proctoscopic appearance, and the development of complications.

Local complications include polyps, stricture, perirectal and perianal complications, hemorrhage, perforation, and an increased susceptibility to carcinoma. The systemic complications may be related directly to the disease or secondary to the nutritional and metabolic disorders secondary to ulcerative colitis. Important among these are nutritional problems, an increased incidence of liver disease, arthritis, and skin complications, notably erythema nodosum and pyoderma gangrenosum.

Although improvement initially is usually noted regardless of the type of therapy employed, there are few data to suggest that any therapeutic agents now in use greatly alter the long-term course of the disease.

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